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Kinsey, Pomeroy and Martin on

SEXUAL BEHAVIOR in the HUMAN MALE

Out of the great amount of discussion centered on this book, one incontestable fact has emerged: the Kinsey Report has great and lasting value for the practitioner of medicine. It is a key to the jumbled maze of truth, half-truth, falsehood and — most deplorable of all — *absolute lack of knowledge* that has thwarted progress in this field from time immemorial. The findings reported here provide a factual basis for understanding *what is normal* and *what is abnormal behavior* for any given patient of any given age, race, educational level and religious affiliation.

By Alfred C. Kinsey, Professor of Zoology, and Wardell B. Pomeroy and Clyde E. Martin, Research Associates, Indiana University. Based on surveys made by members of the staff of Indiana University and supported by the National Research Council with Rockefeller Foundation funds. 804 pages, 6" x 9", with 173 charts and 159 tables. $6.50.

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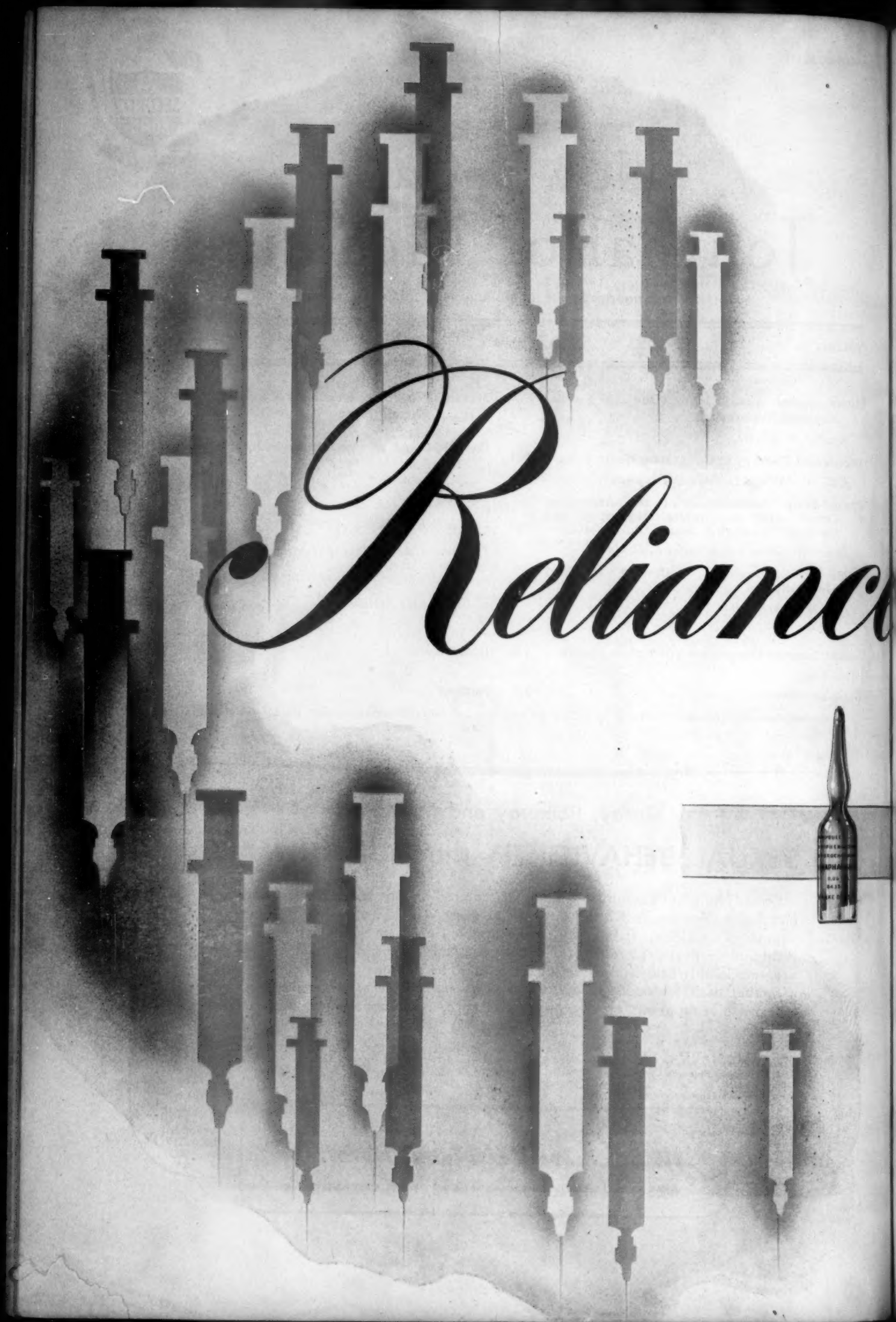
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Volume 239 NOVEMBER 4, 1948 Number 19

ACUTE RENAL INSUFFICIENCY DUE TO LOWER-NEPHRON NEPHROSIS*

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ACUTE renal insufficiency due to the disorder now known as lower-nephron nephrosis[1] or hemoglobinuric nephrosis[2] occurs in association with a large variety of conditions, including intravascular hemolysis associated with transfusion reactions,[3–7] blackwater fever,[8] quinine sensitivity[9] and transurethral prostatectomy,[10, 11] as well as in the crush syndrome,[12–23] nontraumatic muscle ischemia,[24] electrical injury to muscle,[25] heat stroke,[26] uteroplacental damage,[27, 28] after abortion,[29] alkalosis from excessive vomiting,[30] thermal burns,[31, 32] sulfonamide sensitivity [33–36] and from various poisons of diverse origin,[1] including the most common offender, carbon tetrachloride.[37–48]

The purpose of this communication is to present certain data pertinent to this syndrome and to suggest that treatment based on the pathological physiology of this type of renal failure offers considerable promise.

CLINICAL ASPECTS

Irrespective of the antecedent condition associated with this syndrome the clinical features and the histologic pathology appear similar if not identical. With or without an initial period of shock, dependent on the precipitating cause, patients often develop nausea, vomiting, weakness, malaise, sometimes pain in the abdomen or back and, abruptly or insidiously, oliguria or anuria. The magnitude and severity of the general manifestations frequently so divert attention from what at the moment seems a minor matter that it is often difficult to determine just when the urine volume declined or became nil. After renal shutdown, edema generally develops (the magnitude depending on the nature of the treatment), the blood pressure rises, the nonprotein nitrogen steadily mounts, acidosis becomes chemically apparent, and death generally ensues from pulmonary edema or, in certain cases, from potassium intoxication.

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PATHOLOGY

The histologic pathology as noted by Lucké,[1] Mallory[2] and others is essentially as follows: eighteen to twenty-four hours after onset there is lipid vacuolization of the ascending limbs of Henle's loop. Precipitation of pigment casts in the distal convoluted and collecting tubules is generally noted thirty-six to seventy-two hours after onset. This pigment usually gives a positive reaction to benzidine, but does not contain stainable iron. Moderate dilatation of the proximal and sometimes of the distal convoluted tubules follows the pigment precipitation. Sometimes on the third day, and regularly by the fourth and fifth days, necrosis and regeneration of the epithelium in the ascending portions of Henle's loop and in the distal convoluted tubules become evident, and simultaneously lymphocytes appear between the tubules and about the vessels. From the fifth day on rupture of the tubules becomes frequent. There is no significant change in the glomerular capillaries. The capsular space and the lumen of the proximal convoluted tubules may contain a variable amount of amorphous and granular debris. Edema of the interstitial spaces of the kidney is frequently seen. This may well be related to the generalized edema induced by the administration of large quantities of parenteral fluids. The basement membrane of the tubules is usually intact. Available evidence suggests that the re-epithelization of the tubules, albeit imperfect, is completed generally within two weeks of onset.

Although emphasis in the literature has been placed on the anuria and renal pathology it is to be noted that liver damage also occurs.[2, 3, 8, 9, 12, 20, 21, 26, 32, 33, 36] Bywaters,[49] one of the original describers of the crush syndrome, has recently reported central or midzonal liver-cell necrosis following crush or other skeletal injury in 42 patients, the majority of whom died in uremia. In carbon tetrachloride poisoning liver damage is so constant that many physicians are surprised that renal failure often overshadows the hepatic injury.[48]

Survival Time and Cause of Death in Fatal Cases

Lucké[1] has determined the survival time in 100 fatal cases of lower-nephron nephrosis. Ninety-five per cent of the patients succumbed within fourteen days, 86 per cent within ten days, and 48 per cent within six days. No deaths occurred after twenty days. Burwell, Kinney and Finch[7] reviewed 89 cases of oliguria following intravascular hemolysis. Fifty-one of the 55 patients in the fatal cases succumbed within the first two weeks — 26 within six days. The other 4 deaths occurred on the six-

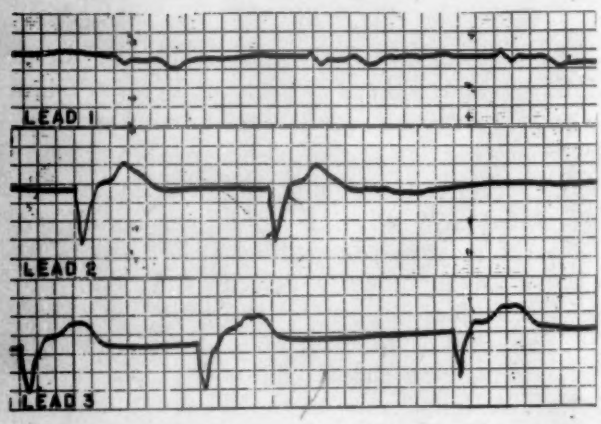

Figure 1. *Electrocardiogram in Case 4 Shortly before Death.*

teenth, seventeenth, eighteenth and twentieth days respectively.

That factors probably unrelated to the kidney may be of very considerable importance in many fatal cases is suggested by the large number of deaths (50 per cent) within the first six days. It appears highly unlikely that renal insufficiency per se would ever lead to death within such a brief period. There is no doubt that the underlying or precipitating condition is frequently the major cause of a fatal outcome, and it is also probable that in some cases the hepatic damage is significant. Massive generalized edema, as well as pulmonary edema, is a common finding at autopsy,[1, 2, 50] the pulmonary form often being the immediate cause of death. Until the last year all the patients in the fatal cases of hemoglobinuric nephrosis observed by me died with, and probably from, pulmonary edema.

The level of the blood nonprotein nitrogen seems to bear little correlation with the outcome. Lower values are more often encountered in fatal cases than in patients who ultimately recover. The blood nonprotein nitrogen of 2 recently studied patients who recovered reached 225 and 255 mg. per 100 cc. respectively whereas in 5 fatal cases the highest values were 115, 154, 182, 195 and 240 mg. per 100 cc. In Lucké's[1] series the nonprotein nitrogen levels in 10 fatal cases were, in ascending order of magnitude, 109, 114, 150, 175, 188, 218, 225, 240 and 265 mg. per 100 cc.

Several investigators[1, 19, 23, 29] have commented on the possible role of potassium intoxication in the fatal outcome through alterations of cardiac function. In 1 case (Case 4) typical electrocardiographic changes of hyperpotassemia preceded death (Fig. 1). Winkler and his associates[51] have shown that if potassium salts are injected intravenously in dogs rapidly enough to raise the serum potassium level a reproducible series of electrocardiographic changes occurs, terminating in death from ventricular flutter, fibrillation or arrest when the level reaches 14 to 16 milliequiv. per liter. At a serum potassium level of 5 to 8 milliequiv., the T waves become tall and peaked; at 8 to 9 milliequiv., the ST interval is depressed, and the T waves become diphasic. The P waves decrease in size and disappear at 9 to 11 milliquiv. per liter, and at the same level intraventricular block occurs. Orally administered potassium salts fail to elevate the serum potassium level significantly in the dog with normal renal function.[52] However, if renal insufficiency has been produced, the same sequence of electrocardiographic changes follows the oral administration of potassium when the serum levels rise.[52] In dogs experimentally rendered anuric, similar electrocardiographic changes follow the increasing concentration of potassium in the blood that occurs as a result of endogenous protein catabolism.[53] There is thus considerable evidence that potassium intoxication is important in certain cases of lower-nephron nephrosis.

Onset of Diuresis in Surviving Patients

In 34 cases of hemoglobinuric nephrosis reported by Burwell, Kinney and Finch[7] in which the patients recovered diuresis began from the second to the twelfth day in 32 and began on the fourteenth and sixteenth days in 2 cases. In the 4 cases reported by Humphrey and Avery Jones[29] diuresis began on the thirteenth to the fifteenth day after the onset of anuria. The patients in Kugel's[50] cases began passing appreciable amounts of urine on the ninth and tenth days. The 2 patients who recovered in the cases presented below had spontaneous diureses on the tenth and fifteenth days of anuria. Many other cases of spontaneous diuresis in the second and third weeks after the onset of anuria may be found. The evidence, therefore, is suggestive that in lower-nephron nephrosis with anuria or oliguria the damage is not always irreversible, and regeneration of the tubular epithelium is possible and may be anticipated in the majority of cases within the first two or three weeks if the patient can be kept alive long enough for healing to occur.

Once recovery from the acute episode has taken place, complete physiologic restitution may be expected to occur over a period of several months.[7, 29, 50]

Maximum Survival Period Without Renal Function

It is currently believed that after complete renal shutdown man can survive at most two or three weeks. This belief has developed during recent years when the parenteral administration of fluids became a routine procedure for a great variety of conditions. In an endeavor to ascertain how long patients with complete anuria survived prior to the days of parenteral fluids the older literature was studied.[54–59] It was not altogether surprising to find that many patients were reported as surviving from three to four weeks, 1 for five weeks, 2 for six weeks, and 3 for seven weeks. Since the possibility exists that certain of these observations were in error it is worth calling attention to 5 of these reported cases in particular in which there appears to be little probability that any urine was formed during the period of observation. In the first of these removal of the right kidney was performed for carcinoma of the kidney twenty-seven and a half days before death.[55] Autopsy revealed the congenital absence of the left kidney. In the second case the patient survived removal of the right kidney for hydronephrosis for twenty-three days before post-mortem examination disclosed the congenital absence of the left kidney.[58] A third patient who died after twenty-five days of anuria was shown at autopsy to have both ureters completely obstructed by cancer.[55] The left kidney was represented by a thin-walled cyst, and the right by a hydronephrotic sac containing a pint of urine. The fourth patient had had chills and fever together with anuria for three days at the age of thirty-two and for eleven days a year later, with recovery associated with the passage of pus-laden urine.[56] At the age of thirty-four, after twenty-two and a half days of anuria during which she was closely observed to make certain that there was no deception, she was operated upon. The left kidney was absent, and 500 cc. of thick, foul-smelling pus was evacuated from the right kidney pelvis. Many stones were found in the calyxes and one calculus completely occluded the right ureter. Recovery was uncomplicated. The fifth patient succumbed thirty days after the onset of complete anuria due to obstruction of both ureters by pelvic carcinomatosis.[57]

Animal experimentation has been somewhat misleading. It has frequently been observed that guinea pigs and rats die a few days after bilateral ureteral ligation[59] or after anuria has been produced by occlusion of both renal arteries for two hours.[60] The survival of rabbits[61, 62] and of dogs[63–65] is somewhat longer, whereas sheep and goats generally do not succumb for two weeks.[59] Presumably, elephants might well survive for months. The increased ability of larger animals to survive without functioning kidneys may in part be ascribed to the fact that the rate of formation of metabolic waste products is a function of the rate of total body metabolism, which in turn is correlated with surface area. The amount of body water, however, in which these products may be distributed and thus diluted is almost a linear function of body weight. This penalty of small size has also been noted in infants and children, and has been commented upon by Gamble.[66]

Theoretic Considerations in Treatment

At this point it may be well to consider the course of events that may ensue in an otherwise healthy adult man weighing 70 kg. who suddenly lost all function of both kidneys but who did not suffer from "toxic destruction" of body protein.[67] There would be a daily insensible loss of approximately 1000 cc. of water by evaporation from the skin and lungs.[66] In the absence of actual sweating no appreciable amount of electrolyte would be lost. Gastric intolerance for food would probably appear and preclude nutrition by mouth, leading to the rapid exhaustion of the scanty body stores of carbohydrate. Approximately 70 gm. of body protein would then be broken down daily,[68] and the remaining caloric need supplied by the burning of about 200 gm. of body fat. In the course of this catabolism of fat and protein, ketone acids, nitrogenous waste products, potassium, sulfate and phosphate would accumulate in the body. Preformed water and water of oxidation in the amount of 470 cc. daily would be released, leaving an approximate daily deficit of 530 cc. The nitrogenous waste products would be distributed throughout the entire body water of approximately 50 liters and would rise steadily, as would the level of potassium in the body fluids. The accumulation of ketone acids as well as sulfate and phosphate anions would be followed by a reduction in the carbon dioxide content of the plasma. Rising plasma phosphate may be accompanied by a lowering of the calcium. However, the presence of acidosis should protect the patient from actual tetany. The daily negative water balance, increasing the osmotic pressure of the extracellular fluids, would lead to cellular dehydration. The duration of life under these circumstances is uncertain. It appears likely that the rise in serum potassium would lead to fatal cardiac changes before nitrogen retention or acidosis became threatening.

If isotonic electrolyte solution is given parenterally concentration of the extracellular electrolytes with secondary cellular dehydration will nevertheless occur by virtue of the evaporation of electrolyte-free water from the skin and lungs. If, on the other hand, sufficient distilled water is admin-

istered to replace the water loss, concentration of the electrolytes in the body fluids should be kept reasonably constant. If, further, 100 gm. of glucose was given daily, ketosis would be prevented and protein breakdown would be reduced by almost half as demonstrated by Butler et al.[68] and by Winkler and his co-workers[69] in their studies of fasting man. This would mean that the nitrogenous waste products, potassium, sulfate and phosphate released by protein catabolism would accumulate at only half the rate that they would have accumulated if glucose had not been received. How rapidly should the nonprotein nitrogen rise in this hypothetic person who is now receiving 100 gm. of glucose a day and whose insensible loss of water is taken care of? The metabolism of 37.5 gm. of protein daily will lead to the formation of 6000 mg. of nonprotein nitrogen, which will be distributed throughout the entire body water (amounting roughly to 50 liters), and therefore the blood nonprotein nitrogen should rise at a daily rate of 12 mg. per 100 cc. By similar calculations it is possible to determine that the daily rise in serum potassium, sulfate and phosphate will be respectively 0.324, 1.86 and 1.66 milliequiv. per liter, on the assumption that the potassium will be distributed in a volume equivalent to the total body water,[53, 70] and that the sulfate and phosphate are distributed only in the extracellular water. Actually since some portion of the phosphate will be deposited in bone or other tissues the rise of serum phosphate will be much slower.

Such data as are available suggest that these rates of increase for nonprotein nitrogen, potassium and sulfate are correct,[29] although the rise in potassium may be slower than expected, possibly owing to an increase in the nonionized fraction of intracellular K-proteinate.[71] Serum sodium levels show no marked deviation from the normal range. Observed serum chloride and bicarbonate values have been lower than those anticipated from the rise in sulfate and phosphate. In a case in which sufficient data were obtained to allow calculation of the electrolyte balance[29] the sum of the anions—$Cl' + HCO'_3 + PO''_4 + SO''_4 +$ protein—was consistently lower than that of the cations—$Na^{\cdot} + K^{\cdot} + Ca^{\cdot\cdot}$. No explanation for this discrepancy was apparent.

Treatment

The treatments that have been suggested in the management of acute anuria or oliguria are many and diverse. They include spinal anesthesia, splanchnic block, diathermy to the kidney region, x-ray irradiation of the kidneys, acetyl-beta-methylcholine injections, irrigation of the renal pelvis, decapsulation or capsulotomy of the kidney, transfusion of compatible blood or plasma, or both, intravenous sodium sulfate, intravenous hypertonic fluids, including glucose and saline solution, massive intravenous administration of saline or lactate solutions, peritoneal lavage and the use of an artificial kidney. Recently enthusiasm for capsulotomy has been noted.[72, 73] J. T. Peters[74] has advanced the theory that anuria is due to edema of the kidney, which produces an increase in the intrarenal pressure, effectively preventing the flow of urine. The fact remains that in patients who recover diuresis starts at the height of fluid retention and thus at a time when the edema of the kidney may be anticipated to be at its greatest. Furthermore, there is no evidence for the existence of edema of the kidney at the onset when the anuria first occurs. The subject of capsulotomy has recently been reviewed,[75] and the evidence in its favor found wanting. It is to be noted that most of the successes reported in the literature indicate that the operation was performed between the eighth and the tenth day, which is the period in which spontaneous diuresis most often occurs. It is of particular interest that in Talbott's[76] case, in which operation was performed on only one kidney, but catheters placed in both ureters, diuresis began at precisely the same time on each side.

There is no doubt that peritoneal lavage can successfully remove large amounts of nitrogen from the body.[65, 77–82] However, the difficulties involved in maintaining water balance and the frequent development of peritonitis have caused some workers[81] to discard this method of tiding the patient over the period needed for tubular regeneration. The artificial kidneys developed by Kolff[83] and Alwall[61, 62, 84] offer considerable promise for the future. However, evidence available at present indicates that the number of patients with lower-nephron nephrosis who will require such management may be materially reduced by the more widespread use of the conservative therapy of restricted fluids and glucose administration. Although Wakeman et al.[85] advocated such a procedure a decade and a half ago, Kugel[50] was unable to find any case of acute toxic nephrosis so treated. He treated 2 patients by rigidly limiting their fluids and obtained uneventful recovery. Since then Muirhead and his associates[81] and Burnett[86] have recommended similar treatment.

The therapeutic regime employed in the treatment of all patients with anuria or oliguria from lower-nephron nephrosis at the Cushing Veterans Administration Hospital has been divided into three phases:

If shock or dehydration is present in the initial phase of this syndrome, whole blood, plasma or saline solution is employed to combat these phenomena.

The second phase of treatment begins when it is observed that the urine volume is markedly diminished or anuria has occurred. Then 750 cc. of 15 per cent glucose in distilled water is given

by vein daily, care being taken to run this in slowly, with every precaution to avoid thrombosis of veins. If necessary a vein is cut down upon. Nothing is given by mouth since vomiting appears to be increased by the oral administration of food or liquid. If there is significant vomiting the amount is carefully measured and that much physiologic saline solution is added to the daily infusion of dextrose in water. During the second week of treatment great fortitude is required because of the insistent demands that the patient be drowned with large volumes of intravenous fluid. This must be resisted. If acidosis becomes clinically manifest (as well as being evident on laboratory examination) a liter of one-sixth molar sodium lactate is given, the extracellular fluid volume being thus expanded as the price for combating acidosis.* Electrocardiograms are made at least every other day for the observance of changes indicative of an excess of potassium. It is my hope at present that it may be possible to combat this if it occurs, by the insertion of a modified Miller–Abbott tube into the small intestine and the perfusion through it into the proximal jejunum of a slightly hypertonic, potassium-free electrolyte and dextrose solution, which is withdrawn from the distal ileum, where its potassium content should be in equilibrium with the blood plasma. With such a procedure Maluf[88] has been able to achieve blood urea clearances of 32 cc. per minute. Any loss of sodium is then replaced intravenously with either potassium-free Ringer lactate or one-sixth molar sodium lactate solution.

When the stage of diuresis appears in the second or third week the third phase of treatment is employed, which consists in administration of a volume of water sufficient to make up for the total urine volume in addition to 1000 cc. for insensible loss as well as any other losses, together with the amount of sodium chloride found in the preceding day's urine. Frequently, during the phase of diuresis, moderate to severe anemia is noted. This is treated by the transfusion of carefully matched blood. If the patient's anuria has been due to a hemolytic transfusion reaction the greatest of care is exercised in the administration of blood although with proper precautions this is a safe procedure. In the state of diuresis the kidney is producing an only slightly modified glomerular filtrate as urine, which may show only a twofold or threefold concentration of nitrogen and very little ability to conserve sodium chloride. Accordingly, salt depletion must be avoided. Furthermore, at this time when the urine volume may be well in excess of 2 or 3 liters daily, the danger of drowning the patient has become remote.

*If any degree of base dilution has occurred from the excessive intake of water, 5 per cent sodium bicarbonate solution may be employed. Not infrequently when first seen these patients have already received large quantities of water by mouth or fluids of low-salt content parenterally and as a result may exhibit significant hypotonicity of expanded body fluids. Such salt depletion, even in the presence of edema, may be greatly benefited by the intravenous administration of 3 to 5 per cent sodium chloride, with or without bicarbonate.[87] It should be emphasized that in these patients the tonicity of the blood cannot be estimated with accuracy from the serum chloride and bicarbonate.

Case Reports

In the following cases the lower-nephron nephrosis was treated by intravenous administration of large volumes of saline solution. Death from pulmonary edema ensued.

Case 1 (C.V.A.H. 578). A 40-year-old man, 2 days after drinking with a friend (Case 2) on November 28, suffered nausea and vomiting, followed by a steadily falling urinary output. Approximately 2 liters of 5 per cent dextrose in physiologic saline solution was administered by vein daily. The urine specific gravity was 1.010, with a + test for albumin, and there were a few red and white blood cells in the sediment. The blood nonprotein nitrogen was 72 mg. per 100 cc. on December 2 and 115 mg. on December 7. The carbon dioxide capacity was 15.3 milliequiv. per liter on December 7.

The urinary output during the last 24 hours was 2000 cc. Autopsy revealed central necrosis of the liver, lower-nephron nephrosis, two 0.6-cm. ulcerations in the duodenum, pulmonary edema and bilateral hydrothorax, with 300 cc. of fluid in the left and 400 cc. in the right pleural cavity. The left lung weighed 1300 gm., and the right 1250 gm. Microscopical examination showed the alveoli to be filled with edema fluid. Examination of the viscera was negative for poisons of the heavy-metal group.

Case 2. (C.V.A.H. 396). A 36-year-old man, 2 days after drinking with a friend (Case 1) on November 28, noticed nausea and vomiting together with tremulousness and hallucinations. From December 1 to 4, inclusive, 9000 cc. of 5 per cent dextrose in physiologic saline solution was given intravenously in the face of a falling urinary output. Periorbital ecchymoses appeared spontaneously on December 3 and spread over the chest on December 6. Edema of the face and extremities was noted on December 4 and of the lungs on December 5. The urine specific gravity was 1.015, with an acid reaction and a +++ test for albumin and a few red and white blood cells in the sediment. The blood nonprotein nitrogen was 157, 162 and 195 mg. per 100 cc. on December 4, 5 and 6. The plasma chloride was 87, and the carbon dioxide capacity 8.5 milliequiv. per liter on the day of death (December 6). The blood prothrombin was 30 per cent of normal, the Lee–White coagulation time 19 minutes, and the bleeding time 2 minutes. No fluids were given on December 5. Death occurred 6 hours after intravenous infusion of 1000 cc. of physiologic saline solution in addition to 500 cc. of one-sixth molar sodium lactate.

No autopsy was performed.

In the following case of lower-nephron nephrosis following an extensive brain hemorrhage, pulmonary edema was controlled by rigid restriction of fluids.

Case 3 (C.V.A.H., 4601). A 29-year-old man was subjected to a second craniotomy and exploration of the third ventricle on January 16. Two transfusions of blood were given. During the next 3 days the temperature increased to 106°F., and a period of hypotension lasting 18 hours occurred. Consciousness was never regained after operation. From January 20 to 23 inclusive the patient received 4000 cc. of 5 per cent dextrose in distilled water and 4000 cc. of 5 per cent dextrose in physiologic saline solution intravenously. From operation until January 20 he was incontinent of an unknown amount of urine. Thereafter he was completely anuric. On January 23 both lungs were filled with moist rales. During the next 7 days he received 750 cc. of 15 per cent dextrose in distilled water by vein daily, with the gradual complete clearing of all signs of pulmonary edema. The blood nonprotein nitrogen rose from 96 mg. per 100 cc. on January 21 to 182 mg. on January 28; the plasma chloride fell to 81.2, and the carbon dioxide capacity to 10.4 milliequiv. per liter. Death occurred on January 30 (1 week after the restriction of fluids).

Autopsy revealed a normal degree of hydration throughout the body. The left lung weighed 450, and the right, 500 gm. There was no evidence of pulmonary edema. Lower-nephron nephrosis was present. A large operative defect in the right frontal lobe of the brain was filled with a blood clot, which extended across the midline to obliterate the basal ganglions on the left and to involve the corpus callosum and insula. The blood clot measured approximately 130 cc. Numerous cysts lined with a single layer of endothelial cells occupied the right thalamus, hypothalamus, midbrain and pons. Blood was present over both hemispheres and the base of the brain.

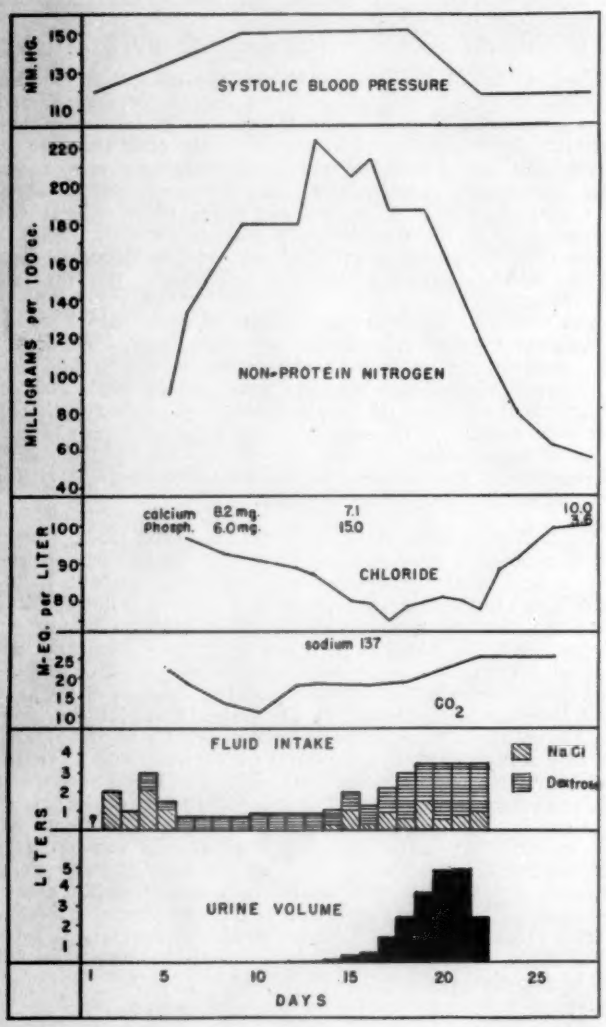

FIGURE 2. *Essential Data in Case 6.*

In the following case the lower-nephron nephrosis was self-treated by fluid restriction. Death with the electrocardiographic changes of hyperpotassemia occurred. There was no pulmonary edema.

CASE 4 (C.V.A.H. 3857). A 52-year-old man had partaken freely of whisky on May 30. He denied the ingestion of any unusual beverages or foods. On June 2 he felt weak, complained of pain in his back and noted a diminished urinary output. Anorexia, nausea and some vomiting began on June 4. He took no food whatsoever and restricted his fluids to less than 1000 cc. daily. The urinary output diminished steadily. When, on June 9, it was less than 2 oz., the patient became alarmed and sought hospitalization. Physical examination was negative except for hypertension, the blood pressure being 160/110. The lungs were clear. The urine was neutral, with a specific gravity of 1.012, a ++ test for albumin and red and white blood cells in the sediment. The blood nonprotein nitrogen was 185 mg. per 100 cc., rising to 240 mg., and the serum chloride 85.5 milliequiv. per liter, falling to 80.3 milliequiv.; the carbon dioxide capacity was 13.8 milliequiv. per liter, falling to 8.5 milliequiv. before death on June 11. Treatment was limited to the administration of 1800 cc. of 15 per cent dextrose in distilled water intravenously during 40 hours in the hospital. Three electrocardiograms were taken. On June 9 the P waves were low, the QRS complexes widened and slurred, and the ST intervals depressed. The QT interval was 0.36 second. On June 10 the P waves were absent, the T waves were tall and wide, and the QT interval was 0.52 second. Shortly before death on June 11, there was an idioventricular rhythm with a rate of 32, the QRS complexes measured 0.20 second, and the QT interval was 0.92 second (Fig. 1).

Autopsy showed lower-nephron nephrosis and central necrosis of the liver. The pleural cavities each contained 250 cc. of fluid. The left lung weighed 660 gm., and the right 600 gm. Microscopical examination disclosed atelectasis of the left lower lobe and a small infarct in the right lower lobe but no significant pulmonary edema.

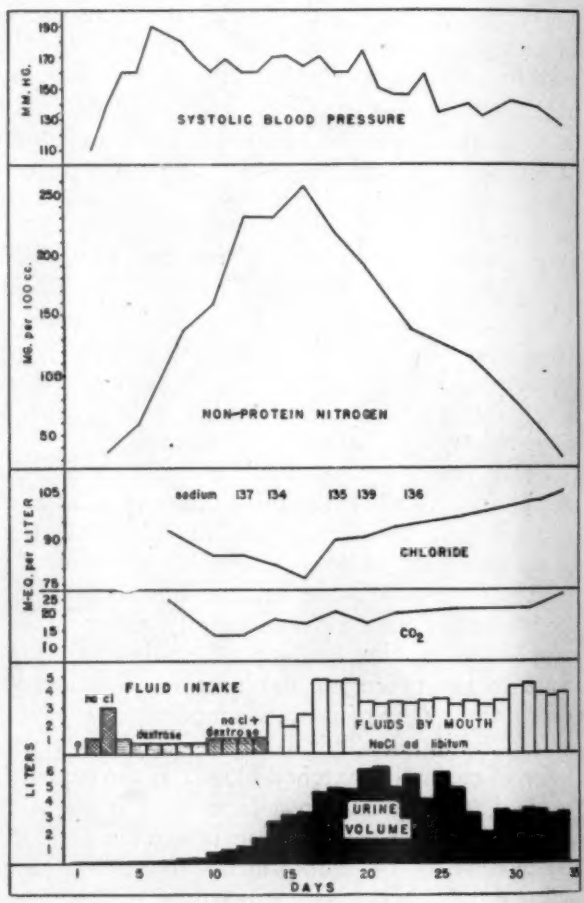

FIGURE 3. *Essential Data in Case 7.*

The following case of lower-nephron nephrosis was complicated by severe hypertension and nitrogen retention. The urinary output was normal.

CASE 5 (C.V.A.H. 6331). A 35-year-old man developed anorexia, nausea and vomiting several days after drinking to excess on October 12, followed by pain in the lumbar region

on October 16 and two convulsive seizures on October 17, after which he was admitted to the hospital.

Two years before admission he had begun to have convulsive seizures occurring at intervals of several months. Eight months after the first seizure his skull was fractured when struck by an airplane propeller. He was unconscious for an unknown period and was hospitalized for a fortnight.

On admission to this hospital the patient was agitated, confused and hallucinated. Numerous ecchymoses were observed over his body. The blood pressure was 220/120. The ocular fundi were normal. All deep tendon reflexes were hyperactive. The urine volume averaged 2000 cc. daily. The specific gravity varied from 1.006 to 1.010, a + test for albumin was constantly observed, and red and white blood cells were present in the sediment on all examinations. The spinal fluid was under normal pressure but showed over 5000 red cells per cubic millimeter. On October 22 the blood nonprotein nitrogen was 175 mg. per 100 cc., falling to 154 mg. 2 days later, when the serum chloride was 73.3 milliequiv. and the carbon dioxide capacity 14.7 milliequiv. per liter. The blood pressure during his 8 days in the hospital varied from 176/98 to 220/140. A convulsion on October 23 was followed by increased clouding of the sensorium. Several small flame hemorrhages developed in the left retina, and the arteries were observed to be contracted. An electrocardiogram on October 22 was normal. The QRS complexes measured 0.07 second. Two days later the P waves were wider, the PR interval was 0.21 second, the QRS complexes widened and slurred (0.11 second), and the T waves tall and peaked. Death occurred on October 25.

Autopsy revealed central necrosis of the liver and lower-nephron nephrosis, with no evidence of antecedent renal disease. The lungs were free of edema, the left weighing 250 gm. and the right 200 gm. There was a depressed fracture of the left parietal region of the skull with an area of brain necrosis 3 cm. deep beneath it.

The following cases of lower-nephron nephrosis were treated by fluid restriction and dextrose administration.

Case 6 (C.V.A.H. 865). A 28-year-old man, while drinking in a hotel bar on March 9, became nauseated and began to vomit. He continued to vomit during the 5 succeeding days and passed no urine after March 10. From March 11 to 14 inclusive he received intravenously 6000 cc. of 5 per cent dextrose in physiologic saline solution and 1500 cc. of 5 per cent dextrose in distilled water. On admission to the Medical Service on March 14 the blood nonprotein nitrogen was 90 mg. per 100 cc., and the carbon dioxide capacity 22 milliequiv. per liter. At this time edema of the face and extremities was present. For the next 2 weeks the patient received nothing by mouth, with the rapid subsidence of excessive vomiting, so that only 100 to 200 cc. was regurgitated daily. Two hundred gm. of dextrose was administered by vein daily, dissolved in 750 cc. of distilled water with an additional amount equal to the preceding day's loss in vomitus. With the onset of diuresis he received an additional amount of physiologic saline solution approximately equivalent to the preceding day's urinary chloride output. (The frequent thrombosis of veins that occurred with the concentrated dextrose has since caused the use of any solution stronger than 15 per cent to be abandoned; in addition the evidence cited above[68] indicates that 100 gm. of dextrose is almost as effective in reducing protein catabolism as 200 gm.) The essential data obtained in this patient are shown in Figure 2. Recovery was uneventful. Urine passed after the onset of diuresis was of a fixed specific gravity at 1.010 and contained albumin and red and white blood cells.

Case 7 (C.V.A.H. 6969). A 40-year-old man was drinking on October 18. On the following day he had severe vomiting and weakness of his right arm and leg of a peripheral neuritic type, possibly associated with the fact that he had been lying on the floor for some hours in a comatose state. During the day an unknown amount of urine was passed, the specific gravity of which was 1.010; the sediment contained albumin and red and white blood cells. Subsequently, he was anuric. During the first 2 days of anuria he received 4000 cc. of 5 per cent dextrose in saline solution and 1000 cc. of 5 per cent dextrose in distilled water on the 3rd day. At this time, when first seen, he had moderate generalized edema. For the next 5 days he received 750 cc. of 15 per cent dextrose in distilled water by vein daily. No thrombosis occurred. With the onset of diuresis on the 9th day he was given 1000 cc. of physiologic saline solution containing 100 gm. of dextrose daily for 4 days, with the subsequent increase in his generalized edema and the appearance of moist rales throughout both lungs. On the night of the fourth day he had a generalized convulsion in which he fractured his left humerus. The serum calcium at this time was 9.3 mg. per 100 cc. After this episode he appeared much improved and was able to take fluid and food by mouth. Although his intake rose to almost 5 liters, his diuresis kept pace with this. The pulmonary and generalized edema subsided, the blood nonprotein nitrogen fell, the serum chloride and carbon dioxide capacity rose, and he made an uneventful recovery. The essential data are shown in Figure 3. Nitrogen clearance was estimated after the onset of diuresis from the 24-hour output of nonprotein nitrogen in the urine and the blood nonprotein nitrogen. From 1.23 cc. per minute on the 10th day of illness it rose steadily to 27.6 cc. 4 weeks later. A week after this the standard urea clearance determined in the usual fashion was 70 per cent of normal.

Summary and Conclusions

The precipitating factors, clinical and chemical aspects and pathologic histology of lower-nephron nephrosis are reviewed.

Evidence is presented suggesting that neither nitrogen retention nor acidosis is responsible for the usual fatal outcome.

Fatal cases of lower-nephron nephrosis often exhibit generalized and pulmonary edema at autopsy, the pulmonary edema frequently being the immediate cause of death.

In the absence of pulmonary edema there is evidence that potassium intoxication may lead to a fatal outcome.

Available data indicate that man, unlike small animals, may survive without renal function for four or more weeks, if excessive quantities of fluids are not administered parenterally.

Histologic and clinical evidence indicates that the tubular lesion is often reparable, with spontaneous diuresis to be expected within three weeks if the patient can be kept alive this long.

A review of the many treatments proposed for this condition fails to reveal evidence that any of them speeds the appearance of spontaneous diuresis.

A regime is outlined, consisting essentially in the replacement of water loss and the furnishing of 100 gm. of dextrose daily, which it is believed may, in many cases, permit the patient to survive long enough to have spontaneous recovery.

Seven cases illustrating various phases of this syndrome and its treatment are reported.

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DICUMAROL THERAPY IN CONGESTIVE HEART FAILURE*

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AMONG the more serious threats to the life of the decompensated cardiac patient are thrombosis and embolism, and some means of combating these phenomena are a very pressing need in cardiovascular therapeutics. Recent work with anticoagulant agents[1, 2] in postoperative patients, in cases of myocardial infarction and in cases of thrombophlebitis suggests that the use of dicumarol offers a safe and effective method of preventing such accidents. To test the effectiveness of this drug, all patients admitted to the Veterans Administration Hospital, Minneapolis, because of cardiac decompensation have been treated with dicumarol since October, 1946. The present report is a preliminary evaluation of the therapy as carried out up to August, 1947.

Although a clear description of hemorrhagic pulmonary infarcts was given by Laennec,[3] it was Virchow[4] who first proposed the view that these lesions were actually due to embolism of branches of the pulmonary artery and who suggested that stasis of the pulmonary circulation was a factor of some pathogenic importance. Experimental support for Virchow's views was supplied by Zahn,[5] who found that sterile mercury emboli, injected into the jugular vein, failed to produce hemorrhagic pulmonary infarcts in rabbits unless the thorax of the experimental animal was tightly bound within two days of the introduction of the embolus. Karsner and Ash[6] reported that obstruction of a branch of the pulmonary artery caused some circulatory changes in the lung tissue supplied by that branch but produced a hemorrhagic infarct only if stasis was effected by simultaneous ligation of the vein from the area.

From these earlier concepts grew the view, now generally accepted, that congestive heart failure predisposes to the development of thrombi in the veins or in the heart itself. These thrombi in time may give rise to infarcts, particularly in the lung, but also in other vital organs such as the brain and kidneys. It is of interest that although Laennec had no adequate concept of the pathogenesis of hemorrhagic infarcts of the lungs, both the illustrative cases he presented in his original description of the lesion were cases of severe congestive heart failure. In recent years a number of surveys have shown conclusively that pulmonary infarcts occur extremely frequently with congestive heart failure and possibly more frequently with this condition than with any other single disease. Hampton and Castleman[7] reported a series of 370 cases of pulmonary embolism and infarction at autopsy. One hundred and eleven were cardiac cases, and of these, 90 per cent showed infarcts of the lungs. Of the noncardiac medical cases, 62 per cent showed infarcts of the lung, whereas in only 58 per cent of the postoperative cases were pulmonary infarcts found. Hines and Hunt[8] observed that 81 (34.6 per cent) of a series of 234 cardiac cases at autopsy showed gross pulmonary infarcts, although this lesion had been diagnosed clinically in only 2 of the 81 cases. Greenstein[9] reported pulmonary emboli in 50 per cent of 32 cardiac cases at autopsy. Kinsey and White[10] reviewed 200 cases of congestive heart failure to ascertain the cause of the fever often seen in this disease. They described three grades of cardiac failure: left ventricular failure alone; moderate right ventricular failure (enlarged liver with slight to moderate dependent edema); and marked right ventricular failure with anasarca. Their Grades II and III conform almost exactly with the cases making up the present series for which reason their statistics have been recomputed leaving out their Grade I (left ventricular failure alone). Table 1, constructed from their data, shows the incidence of pulmonary infarcts in the autopsied, the dead but not autopsied and the surviving members of the series. In a series such as theirs, and our own, the true incidence of pulmonary infarction probably lies somewhere between the minimum (clinical) figure of 13 per cent and the maximum (autopsy) figure of 40 per cent. That many infarcts of the lungs and of the other organs such as the kidney and spleen are never suspected clinically cannot be denied; yet one cannot accept the incidence of such lesions at autopsy as the true incidence in all cases of congestive heart failure, since not all persons with congestive failure die

Table 1. *Incidence of Pulmonary Infarcts in Series of Kinsey and White.*[10*]

Type of Case	Total Cases	Cases of Pulmonary Infarct
Autopsy performed	45 (24.4%)	18 (40%)
Death but no autopsy	30 (16.3%)	8 (27%)
Survival of patient	109 (59.3%)	14 (13%)
Totals	184	40 (22%)

*Grades II and III only.

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while under observation. In fact, death may occur partly as a result of multiple embolic phenomena so that the incidence at autopsy, as compared with the incidence in a series of this type, is probably unduly high. We believe that the figure 22 per cent is as close as one can come at present to the true incidence of pulmonary infarcts in patients with congestive heart failure, not all of whom die and none of whom are treated with anticoagulants. The true incidence is almost certainly no lower, and may well be somewhat higher.

Material

To arrive at a preliminary evaluation of the therapy the records of all patients treated were reviewed. Patients with dyspnea and basal rales as the only indication of decompensation were excluded. Minimum requirements for inclusion in the series comprised such signs as hydrothorax, enlarged tender liver, peripheral edema and elevation of the venous pressure. All except a few patients had peripheral edema, and many had anasarca. The total number of cases exhibiting definite congestive failure was 61. On the basis of the criteria of Kinsey and White 20 of our cases fell into Group II and 41 into Group III.

Table 2. *Types of Heart Disease.*

Type	No. of Cases	Percentage
Arteriosclerotic	23	38
Rheumatic	16	26
Hypertensive and arteriosclerotic	11	18
Hypertensive	7	12
Myocarditis, etiology unknown	2	3
Syphilitic	1	—
Congenital defect with bacterial endocarditis	1	—

The ages of the patients in the series varied from twenty-two to eighty-four years, about two thirds being in the group from fifty to fifty-nine years. Ten patients were less than fifty, and 11 were over sixty years of age.

The average stay in the hospital was fifty-three days, the range being from nine to two hundred and ten days. Thirty of the 61 patients were in the hospital from two to six weeks, and 30 for more than six weeks. Only 1 patient was in the hospital for less than two weeks.

The types of heart disease represented in the series are shown in Table 2. There were 7 patients (12 per cent) with acute myocardial infarction and congestive failure; all 7 are included in the arteriosclerotic or hypertensive and arteriosclerotic categories. In 19 cases (31 per cent) auricular fibrillation was present, and there were definite signs of mitral stenosis in 11 (18 per cent). All 3 of these conditions probably predispose, independently of cardiac decompensation, to thrombosis and embolism. In spite of this fact no attempt was made to rule out patients with any of the 3 conditions. Congestive failure was the only basis for selection.

Method

Before a patient was given dicumarol, a careful search was made for contraindications to the use of the drug. According to Allen et al.,[1] these include renal insufficiency, blood dyscrasias that in themselves cause increased tendency to bleed, hepatic disease associated with a decrease in prothrombin concentration, ulcerative lesions of various sorts and operations on the brain or spinal cord after which bleeding might be fatal. The same authors regard subacute bacterial endocarditis as a probable contraindication. If no contraindications were present, a sample of blood for determination of the prothrombin time was withdrawn, and the initial dose (usually 200 mg.) of dicumarol was given orally. In a few cases, small doses of heparin were given intramuscularly in addition to the dicumarol for the first twenty-four or forty-eight hours. Once the administration of dicumarol was begun, the prothrombin time was determined daily, and the dosage of the drug was adjusted accordingly. The aim was to keep the prothrombin concentration below 30 per cent and above 10 per cent, as suggested by Allen and his co-workers.[1] The average initial prothrombin concentration, before dicumarol was started, was 62 per cent of normal, and in 1 case it was only 17 per cent. We interpret this to be further evidence that liver function may be significantly impaired in congestive heart failure. Cotlove and Vorzimer[11] studied the prothrombin time in 20 patients with congestive heart failure and concluded that the disorder does not per se influence the prothrombin time. Their data do not include control prothrombin times and for this reason are difficult to interpret. The present figures provide strong evidence that congestive heart failure may depress the prothrombin concentration (and increase prothrombin time) quite markedly.

The average number of days during which dicumarol was given was twenty-three, the range being from two to fifty-nine. The average duration of adequate dicumarol effect, as judged by the prothrombin time, was thirty-two days, with a range of four to one hundred and two. In most cases the drug was continued until the patient was ambulatory or until death supervened. The average total dose of dicumarol was 2255 mg., and the average daily dose was 105 mg. The latter figure is somewhat misleading in that it is calculated from the number of days on which dicumarol was actually given. Perhaps a more pertinent figure is the average dose per day of adequate dicumarol effect, which was 78 mg. This is in accord with the view that patients in cardiac failure require smaller doses of dicumarol than compensated persons do.[11]

No hemorrhagic complications developed in any of the cases although it was often necessary to suspend dicumarol therapy because of excessive depression of the prothrombin concentration.

Vitamin K (30 mg. intravenously, three or four times daily) was occasionally used to counteract excessive dicumarol effect, but this measure was rarely necessary.

The mortality in the series was 32.8 per cent (20 deaths), and autopsies were done in 12 cases.

Results

Probably the most significant finding in this survey is that there were no deaths definitely attributable to classic pulmonary embolism, and only 1 death might conceivably have been due to such a condition. The patient was an eighty-two-year-old man who had severe arteriosclerotic heart disease and whose electrocardiogram showed left bundle-branch block. His decline was actually gradual but death occurred unexpectedly, and since there was no autopsy one cannot rule out massive pulmonary embolism as the immediate cause of death. In none of the remaining 19 cases was death sudden enough or the terminal symptoms suggestive enough to permit the diagnosis of fatal pulmonary embolism. No such embolus was found in any of the 12 autopsied cases although small emboli were present in several.

The clinical diagnosis of nonfatal embolism and infarction in the lungs is notoriously difficult and in many cases is frankly impossible. Under the best of conditions many infarcts remain silent and undiagnosed. In the present work symptoms and signs were carefully scrutinized for evidence of infarction. In addition, elevations in temperature, pulse rate, white-cell count and sedimentation rate, x-ray films of the chest and urinary-sediment, serum-bilirubin and urinary-urobilinogen determination were specifically studied. Unexplained elevations in temperature, pulse or sedimentation rate probably do not constitute sufficient evidence for the diagnosis of infarction unless accompanied by other evidence such as appropriate symptoms and signs, the visualization of pulmonary lesions by x-ray study or elevation in serum bilirubin or urine urobilinogen. On the other hand, unexplained hematuria, alone or in combination with other evidence, has been taken to mean probable renal infarction.

On the basis of clinical data, definite pulmonary infarcts developed in 2 patients on dicumarol therapy. There is evidence, however, that the dicumarol effect was inadequate before and during the time the embolic phenomena appeared. One of the patients developed thrombophlebitis at a time when dicumarol dosage was adequate, but some days later, when pulmonary infarction occurred, the prothrombin concentration ranged between 30 and 35 per cent. Although these levels are borderline, this case is included in our list of dicumarol failures. The other patient was put on dicumarol therapy because he had previously developed pulmonary infarction. Since there was a rather marked initial drop in the prothrombin concentration, dicumarol was discontinued and was not started again for nine days. During the three days preceding the appearance of fresh infarcts of the lung, the prothrombin concentration ranged between 60 and 70 per cent, and it seems likely that the complication would have been avoided if the dicumarol dosage had been adequate. The case was therefore not included in the group of dicumarol failures. Two patients had transient, microscopic hematuria (2 or 3 red cells per high-power field in a single specimen) while on dicumarol therapy, but in 1 case the infarct, if present, occurred before adequate reduction in the prothrombin concentration had been obtained. In the other case dicumarol therapy was adequate, and the case was accepted as one of dicumarol failure.

Table 3. *Infarcts Found at Autopsy.*

Patient	Type of Heart Disease	Location of Thrombi	Location of Infarct	Occurrence of Infarction
C. A.	Isolated myocarditis	Left ventricle	Right kidney	Before dicumarol treatment
C. V.	Acute myocardial infarct	Left ventricle	Lower lobes of lungs	Before and during dicumarol treatment
C. M.	Arteriosclerotic	Left auricle	Right kidney and spleen	Before dicumarol treatment
C. L.	Hypertensive and arteriosclerotic	Left auricle	Lower lobes of lungs	After dicumarol treatment
B. G.	Rheumatic	Left auricle	Lower lobes of lungs	After dicumarol treatment
J. H.	Hypertensive and arteriosclerotic	Femoral vein	Lower lobes of lungs	Before and after dicumarol treatment

At autopsy infarcts (other than myocardial) were present in 6 out of 12 cases. From the ages of the lesions as judged morphologically, it was possible to determine with reasonable certainty whether the infarcts had occurred before, during or after dicumarol therapy. In 5 cases infarcts had developed either before dicumarol had been given or after it had been withdrawn. In the remaining case pulmonary infarction had apparently occurred in spite of adequate doses of dicumarol. The patient, who was suffering from massive myocardial infarction, developed large mural thrombi and multiple pulmonary infarcts but was so ill that the complication did not become clinically

manifest. Further information on these 6 cases is given in Table 3.

With the clinical and post-mortem evidence combined, it seems probable that embolic phenomena developed in 4 (6.5 per cent) of the 61 cases despite adequate dicumarol therapy. If the comparison between our data and those of Kinsey and White[10] is valid, the difference in incidence of embolic phenomena in the two series (22 per cent in theirs, and 6.5 per cent in ours) is impressive. This difference is statistically significant for samples of these sizes (sigma of the difference = ± 4.4; observed difference = 15.5). It should be noted that we included embolic phenomena of all types in our reckoning, whereas Kinsey and White were concerned only with infarcts of the lungs. If we exclude the case of renal infarction, the incidence of embolic phenomena in our series becomes 4.9 per cent.

Discussion

That congestive heart failure predisposes to the development of thrombosis and embolic phenomena seems established. For this reason the use of anticoagulants in the treatment of the disorder is theoretically fully justifiable. In practice, dicumarol is not only effective as an anticoagulant but also safe if certain routine precautions are observed during its administration.

To establish the efficacy of dicumarol therapy in congestive failure beyond question will require methodical treatment of many hundreds of cases with the drug. Although the present series is not large enough to achieve this result, the fact that there were no deaths attributable with certainty to massive pulmonary embolism is highly suggestive, and the low incidence of embolic phenomena of lesser magnitude is only slightly less so.

From our results we believe that dicumarol therapy is probably effective in protecting the patient with congestive heart failure from the danger of embolism and that controlled anticoagulant therapy may become as important in the treatment of the disorder as it already is in that of thrombophlebitis or of postoperative patients. The protection it affords is apparently not absolute. It seems likely that it retards or prevents the propagation of established thrombi, but it can hardly prevent the breaking off of unorganized projections of a thrombus lying loose in a vessel or chamber of the heart. Ideally, therefore, one should begin dicumarol therapy as early in the disease as possible and should continue it, in the absence of contraindications, as long as signs of cardiac decompensation remain.

Summary and Conclusions

Sixty-one patients with definite congestive heart failure were treated with dicumarol in an effort to decrease the incidence of embolic phenomena.

Previously published reports indicate that in a group of cardiac patients comparable to our own, one may expect embolic phenomena in the form of infarcts of the lungs in at least 22 per cent. In our series, the incidence of such lesions, during the period when dicumarol therapy was effective, was 6.5 per cent. There were no deaths attributable with certainty to massive pulmonary embolism, and only 1 death that might conceivably have been due to such an accident.

On the basis of these results, it is probable that dicumarol therapy gives protection from thrombosis and embolism to the cardiac patient when he needs it most: when he is in congestive failure. Further evaluation of the method is under way.

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CLOSED-LOOP OBSTRUCTION OF THE ASCENDING COLON, WITH INCOMPLETE DESCENT OF THE CECUM, SIMULATING ACUTE CHOLECYSTITIS*

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CLINICAL findings and laboratory tests frequently fail to indicate accurately the pathologic status of the gall bladder in acute cholecystitis. Gangrene with incipient or actual perforation may exist with minimal physical signs and with normal or only slightly elevated temperature and blood counts. For these reasons, and because of the ease and safety of cholecystectomy in the early stages of the disease, early operation is being advocated with increasing frequency.[1–11] The purpose of this communication is to present 2 cases in which acute, closed-loop obstruction of the ascending colon in combination with incomplete descent of the cecum was mistaken for acute cholecystitis, a diagnostic pitfall that may be avoided if both conditions are kept in mind when acute surgical problems involving the right upper quadrant of the abdomen are encountered.

CASE REPORTS

CASE 1. A 47-year-old woman was admitted to the hospital on January 7, 1941, complaining of abdominal pain of 5 hours' duration.

Two years before admission she began to complain of intermittent, dull, nagging pain in the right side of the abdomen, which was indefinitely located at the level of the umbilicus and in the right upper quadrant. She also noted flatulence and a feeling of distention following meals, which was relieved by belching. She had always been constipated, requiring a cathartic once or twice a week. Repeated questioning failed to elicit a history of change in bowel habits or abnormal stools. Three months before admission examination by her family physician revealed mild tenderness in the right middle portion of the abdomen. She was placed on a regimen that included milk of magnesia and mineral oil. Thereafter her bowels moved regularly and the abdominal pain disappeared, but gas and indigestion following food, particularly fatty and fried food, persisted. She was instructed to take a fat-free diet, and 2 months later her weight had fallen from 180 pounds to 166 pounds. This was believed to be due to the low-calorie intake. A Graham test on December 18, 1940, showed no filling of the gall bladder.

About 2 weeks before admission abdominal pain recurred, at this time located in the right upper quadrant, nonradiating and considerably more severe than that during previous episodes. A bile-salt preparation prescribed at this time caused several watery stools a day but did not relieve the abdominal pain. Five hours before admission the patient was awakened by the sudden onset of excruciating pain in the right upper abdomen radiating to the right scapular region and associated with nausea and vomiting. When she was seen at home by the family physician the entire right side of the abdomen was found to be spastic and tender, and she was immediately hospitalized.

Physical examination revealed a well developed, moderately obese woman who complained bitterly of pain in the right upper quadrant. The tongue was dry and furred. The heart was normal and the lungs were clear. The entire right side of the abdomen was tender and spastic, with the point of maximum tenderness about 4 cm. below the costal margin in the midclavicular line. Rebound tenderness was present throughout the abdomen and was referred to the right upper quadrant. No masses were felt. Pelvic and rectal examinations were noncontributory.

The temperature was 98°F., the pulse 90, and the respirations 20.

Each of two urine specimens showed no abnormalities. Examination of the blood disclosed a red-cell count of 4,530,000, with a hemoglobin of 91 per cent, and a white-cell count of 6700, with 61 per cent neutrophils. The icteric index was 9.

An initial diagnosis of acute cholecystitis and cholelithiasis was made, and operation was deferred until the fluid and electrolyte balance could be re-established. During the first 8 hours of hospitalization the abdominal tenderness progressively diminished, her general condition improved, and the white-cell count fell to 5400. At the end of this time she suddenly entered a state of peripheral vascular collapse, with rapid, thready pulse and a blood pressure of 80/60. A poorly defined mass could then be felt in the right upper quadrant. Transfusion of whole blood was started at once, with rapid improvement. It was thought that the acutely inflamed gall bladder had perforated, and, as soon as her condition permitted, she was transferred to the operating room.

At operation the gall bladder was found to be normal. The cecum was incompletely descended and lay in the right upper quadrant. Five centimeters distal to the hepatic flexure was a small annular carcinoma, which completely obstructed the transverse colon. A huge retroperitoneal abscess was found in the right upper quadrant. Its lateral wall, consisting of parietal peritoneum, overlay the colon proximal to this lesion. This abscess was opened, and over a liter of bloody, foul-smelling pus was aspirated. A large area of gangrene was found on the posterior wall of the ascending colon near the hepatic flexure, and in the center of this area was a perforation 2 cm. in diameter. Since it was impossible to close the perforation satisfactorily, the right half of the colon was resected, the terminal ileum and transverse colon being exteriorized. During the operation the blood pressure fell to dangerously low levels in spite of the continuous administration of whole blood. After operation her condition continued progressively to deteriorate, and she died 12 hours later. Permission for autopsy was refused.

CASE 2. A 73-year-old woman was admitted to the hospital on March 28, 1948, with the chief complaint of abdominal pain.

Four years previously she had experienced an attack of fairly severe, right-upper-quadrant pain, which radiated to the right scapular region and which persisted for 24 hours. For 2 days thereafter she was mildly jaundiced but could not recall the color of stools or urine. Thereafter, she remained on a low-fat diet and, except for occasional bloating after meals, had no abdominal symptoms until the night before admission to the hospital. At that time she was awakened by the sudden onset of pain in the epigastrium radiating to the right upper quadrant. The pain was constant and associated with increasing tenderness. On the following morning the patient herself noted a mass in the right upper quadrant. There was no nausea or vomiting, and she was emphatic in stating that her bowels moved daily and that there had been no change in bowel habits and no abnormal stools.

Physical examination revealed a well developed, well nourished woman in moderate distress. There was marked tenderness in the right upper quadrant of the abdomen associated with muscle spasm and some rebound tenderness. A firm, tender mass about 6 cm. in diameter, which descended with inspiration and appeared to be contiguous with the liver, was palpable below the right costal margin.

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The temperature was 98.6°F., the pulse 84, and the respirations 20. The blood pressure was 185/98.

Examination of the blood disclosed a red-cell count of 4,440,000, with a hemoglobin of 14.5 gm., and a white-cell count of 9850 with 84 per cent neutrophils, of which 2 per cent were stab forms. The urine was normal except for a rare pus cell in the sediment. The blood nonprotein nitrogen was 43 mg., and the total protein 6.3 gm. per 100 cc., with an albumin-globulin ratio of 1.4:1. The serum chloride was 491 mg. per 100 cc.

An x-ray film of the chest showed the lung fields to be clear; the heart and great vessels were normal. X-ray study of the abdomen revealed the presence of an ill defined soft-tissue mass in the right upper quadrant, the nature of which could not be determined. The lower pole of the right kidney was well seen and appeared normal. There were no opaque gall-bladder or urinary-tract calculi and no evidence of intestinal obstruction.

The initial diagnosis was acute cholecystitis, and, because of the evidence of peritoneal irritation, it was feared that perforation was imminent. Immediate surgery was therefore advised.

Operation was performed 3 hours after admission. The mass was found to be an incompletely descended cecum, which was greatly distended, but with its lower border above the level of the umbilicus. The colon was found to be obstructed at the hepatic flexure, where there was a small, constricting carcinoma. The serosa of the colon was obviously invaded with cancer at this point, but there were no distinct metastases. The colon distal to the constricting carcinoma was of normal caliber. The ileocecal valve was competent, and the ileum was not distended. The very thin wall of the distended cecum appeared to be viable, and although there was a moderate quantity of cloudy peritoneal fluid in the right gutter, there was no evidence of perforation or peritonitis. Since the ileum proximal to the ileocecal valve and the transverse colon distal to the obstructing neoplasm were both of normal caliber, the entire right half of the colon and the distal 15 cm. of the ileum were resected with an end-to-end anastomosis of ileum to transverse colon. A catheter ileostomy for decompression was placed proximal to the suture line. Primary resection was considered the operation of choice because the incompletely descended cecum did not lend itself well to a cecostomy and, furthermore, cecostomy would have materially interfered with later resection of the neoplasm. An appendocostomy was considered but was impossible because the lumen of the appendix was obliterated.

Postoperatively, convalescence was complicated by a period of obstruction of the small intestine, which was probably due to adhesions and which responded well to intubation. The wound healed by first intention, and the patient was discharged from the hospital on the 23rd postoperative day.

Discussion

Although much has been written on the treatment and prognosis of acute cholecystitis, remarkably little is to be found in the literature on the diagnosis of this condition. This point has been emphasized by Lawrence and Clute[12] in the discussion of 4 cases in which intrinsic diseases of the liver were responsible for the clinical picture usually associated with acute cholecystitis. In 3 of their cases tumors of the liver were found — 2 metastatic, and 1 primary. The fourth patient had acute central necrosis of the liver due to carbon tetrachloride poisoning. The cases presented above indicate that lesions of the colon must also be considered in the differential diagnosis.

The diagnostic confusion between lesions of the colon and acute cholecystitis is dependent upon three factors: the site and type of obstruction; competence of the ileocecal valve; and incomplete descent of the cecum.

Colonic obstruction due to carcinoma usually progresses slowly over a period of several months and most commonly results from lesions located in the left half of the colon. In a series of 150 cases of carcinoma of the colon with complete obstruction reported by Gregg and Dixon[13] there were only 5 cases with the obstructing neoplasm in the cecum or ascending colon. In an additional 19 cases the obstruction was in the hepatic flexure or transverse colon. When obstruction of the colon is sudden and complete the resulting symptoms overshadow those of the chronic obstruction, which have usually been present for some time. Symptoms of chronic obstruction are due to the gradual stenosis of the lumen of the colon by the growing neoplasm. As pointed out by Mayo[14, 15] and Coller and Berry[16] this gradual stenosis may give rise to dyspepsia, with sour eructations and postprandial distress. These symptoms are often referred to the upper abdomen and may closely simulate those associated with gall-bladder disease.

Occasionally, symptoms of preceding chronic obstruction are completely absent, and the first indication of abdominal disease is the sudden, unheralded obstruction of the colon. This type of obstruction was present in 5 of 129 cases of carcinoma of the colon reported by Miller.[17]

Competence of the ileocecal valve is said to be present on routine barium-enema x-ray examination in about 10 per cent of cases.[18] If this valve is incompetent, acute obstruction of the colon results in progressive retrograde distention of the small intestine and the clinical picture usually associated with low intestinal obstruction. However, when the ileocecal valve is competent the distention resulting from acute obstruction of the colon is limited to the colon, and, because of its greater diameter and thinner wall, the distention is most marked in the cecum, regardless of the point at which the colon is obstructed. The degree of distention of the cecum under these circumstances frequently becomes so great that it causes areas of necrosis and eventual perforation.[19–21] The perforation of such a necrotic area was the cause of the sudden onset of shock in Case 1. In Case 2 the distended cecum formed an easily palpable, acutely tender mass, which was mistaken for a distended, inflamed gall bladder.

Rankin[22] has emphasized the fact that necrosis and perforation of the normally placed cecum due to closed-loop obstruction of the colon may give rise to a clinical picture resembling that of appendicitis. During the second trimester of intrauterine life the cecum normally descends from the right upper quadrant of the abdomen to the right lower quadrant. When this descent fails to take place and the cecum remains in the right upper quadrant the distention, necrosis and eventual perforation resulting from acute closed-loop obstruction may give rise to the clinical picture of acute cholecys-

titis. In both the cases presented above the cecum had failed to descend and lay in the right upper quadrant of the abdomen.

The differential diagnosis between acute, closed-loop colonic obstruction with incompletely descended cecum and acute cholecystitis depends primarily upon keeping the former condition in mind when one is dealing with lesions involving the right upper quadrant of the abdomen. It is probable that in a majority of cases a carefully taken history will reveal significant changes in bowel habit preceding the onset of acute symptoms. It should be emphasized, however, that such symptoms may be entirely absent as in the cases presented above. Simple x-ray study of the abdomen, by demonstrating a distended loop of gas-filled colon in the right upper quadrant, may make the diagnosis obvious. Such an examination was not done in Case 1 because of the sudden onset of serious peritonitis associated with shock. In Case 2 an x-ray film of the abdomen failed to reveal the distention of the ascending colon and cecum because the closed loop was filled with fluid and contained relatively little gas. The diagnosis in Case 1 was further confused by the positive Graham test done three weeks before admission. Why the gall bladder failed to fill at this time is not clear.

It is evident that the one procedure that will establish the diagnosis of colonic obstruction is x-ray examination with barium enema. Because the combination of circumstances causing carcinoma of the colon to resemble acute cholecystitis is not commonly encountered, it is unlikely that routine barium enema is necessary when one is dealing with the clinical picture of acute cholecystitis. Since acute obstruction of the colon due to cancer is probably invariably associated with the presence of occult blood in the stool, the guaiac test affords a simple screening method for determining when barium enema is indicated. In the absence of obvious anal or rectal disease the presence of occult blood in the stool should serve as a warning that symptoms of acute cholecystitis may be of colonic origin.

Since acute, closed-loop obstruction of the colon demands early surgery, just as acute cholecystitis does, the importance of emphasizing an accurate preoperative diagnosis might be questioned. Emergency operations are often done at odd hours when operating-room personnel is limited. An accurate preoperative diagnosis will point up the necessity for an adequate team before the abdomen is entered.

Acute closed-loop obstruction of the ascending colon in the presence of an undescended cecum presents a problem in surgical management when the obstructing neoplasm is at or near the hepatic flexure. Since the competent ileocecal valve prevents distention of the terminal ileum in the early stages, primary resection with end-to-end ileotransverse colostomy and proximal decompressing ileostomy, followed by adequate antibiotic therapy, is the choice of many surgeons even in the absence of adequate preoperative preparation of the colon. Such a choice proved adequate in Case 2. As an alternate method the ileum and transverse colon may be brought out on the abdominal wall to form an open ileotransverse colostomy, as advocated by Lahey. Although such a procedure gives added protection against peritonitis, it has the disadvantage of subjecting the wound and surrounding skin to the digestive action of the ileal discharge. If the wall of the cecum is so damaged that it will not withstand the manipulation necessary to a primary resection, a cecostomy for temporary decompression may be necessary although the resulting adhesions will complicate the subsequent resection. Under these circumstances appendicostomy may be the operation of choice. Such a procedure was rendered impossible in Case 2 by obliteration of the appendiceal lumen.

Summary

Two cases are presented in which acute, closed-loop obstruction of the ascending colon in the presence of an incompletely descended cecum gave clinical pictures closely simulating that of acute cholecystitis.

The differential diagnosis depends primarily on keeping the condition in mind when one is dealing with acute problems involving the right upper quadrant of the abdomen. Simple x-ray examination of the abdomen may fail to demonstrate the obstructed loop. The presence of occult blood in the stool should serve as an indication for barium enema x-ray studies when the clinical picture of acute cholecystitis is encountered.

Operative therapy is briefly discussed. The possibility of closed-loop obstruction of the colon should give added impetus to an aggressive attitude on the part of the surgeon confronted with the clinical picture of acute cholecystitis.

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BACTERIAL ENDOCARDITIS FOLLOWING URETHRAL MANIPULATION

Report of Two Cases

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REVIEWS in the older literature[1-3] and a recent article[4] have commented on the frequent occurrence of bacteremia following manipulation of the genitourinary tract. In one report[3] the complication of bacterial endocarditis in a case is noted, but a perusal of the literature since 1940 revealed no recently reported cases. To emphasize the occurrence of this complication and to stress the need for routine prophylaxis in persons with known valvular defects, the following cases of bacterial endocarditis, developing after urethral dilatation and terminating fatally, are presented.

CASE 1. A 56-year-old man was admitted to the hospital on July 6, 1945, with the complaint of chills, fever and vomiting. A few hours previously, sounds had been passed for the relief of urethral strictures. Physical examination was negative; no cardiac murmurs were noted. A retention catheter was inserted, and 20,000 units of penicillin was given intramuscularly every 2 hours for ten doses. The temperature promptly fell to normal, and the patient was discharged 2 days after admission.

Two days later, the patient was readmitted to the hospital with a history of having developed severe chills and fever almost immediately after leaving the hospital. Physical examination revealed a soft, grating systolic murmur at the apex and a few posterior basal rales. He was catheterized; penicillin was given intramuscularly every 2 hours for 2 days in a dosage of 20,000 units and every 3 hours for 2 days in a dosage of 10,000 units. The temperature quickly fell, and the patient was discharged on the 4th hospital day.

Ten days later he was readmitted, with complaints of continued chills, fever, malaise and severe headaches since arrival at home. At this time, no murmur was noted, but a gallop rhythm was present at the apex. No petechiae were observed, and the spleen was never felt. No organic defects were found on cystoscopy and retrograde pyelography on the 3rd hospital day, but colon bacilli were recovered from the bladder and both ureters. On the 9th hospital day several blood cultures were positive for colon bacilli, and purpuric spots appeared over the body. Intramuscular injections of penicillin (20,000 units every 3 hours) were begun at that time, but the patient became moribund and died on the 12th hospital day.

Autopsy disclosed old, inactive rheumatic inflammation of the mitral and aortic valves, with superimposed acute, ulcerative endocarditis of the left auricular endocardium and mitral valve. Post-mortem blood cultures from the heart were positive for colon bacilli. Focal embolic infarctions were seen in the kidney and spleen, and there were chronic, inflammatory changes in the urinary bladder and urethra.

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CASE 2. A 56-year-old man was admitted to the hospital on November 7, 1947, with the complaint of shaking chills and fever for 1 week prior to admission. Three weeks before entry, he had undergone urethral dilatation for strictures, and a few hours later he had an episode of violent shaking chills and fever.

The past history revealed an attack of rheumatic fever as a child, necessitating bed rest for 11 months. Since that time, however, there had been no cardiac complaints.

Physical examination revealed a loud systolic and a harsh diastolic murmur at the aortic area, with much fainter replicas at the apex. No external stigmas of embolization were noted at that time, and the spleen was not felt. The remainder of the physical examination was noncontributory.

On the following day, numerous petechiae were noted on the abdominal wall, and several hemorrhagic bullae appeared on the toes of the right foot. Cultures of these bullae were positive for *Staphylococcus aureus* and were mannite and coagulase positive; three cultures of blood drawn in the first 2 days were positive for the same organism. Intramuscular injection of penicillin (100,000 units every 4 hours) was begun. New bullae appeared on the hands, but the patient improved clinically. Seven days after entry, because of developing cardiac decompensation, the patient was digitalized; a few hours later, the clinical picture of pulmonary embolism was evident. The patient rallied briefly at this point, but 2 days later became comatose and remained so until the time of death, 18 days after admission. Terminally, uremia was present. The penicillin was increased to 100,000 units every 2 hours on the 3rd hospital day, and to 200,000 units every 2 hours on the 5th day. All blood cultures taken after the initial three were negative. No autopsy was performed.

DISCUSSION

The sequence of events in both cases and the similarity of the organism in the blood stream and urinary tract in 1 case make it evident that the endocarditis had a direct relation to the urethral manipulation. Although urethral dilatation is a common office procedure, such complications make it mandatory to consider the use of prophylactic agents in all persons subjected to these procedures. Persons with a clear history and definite signs of rheumatic heart disease must receive vigorous prophylaxis. The method of choice is not yet certain, but the use of penicillin, with or without sulfadiazine, for two days before and after manipulation, has been advised by Glaser et al.[4] and Clark and his associates.[5]

Of interest was the development of signs of a pulmonary embolism immediately after full digitalization in Case 2. Such incidents suggest caution in the use of digitalis in patients who have already manifested minor embolic phenomena.

Summary

Two cases of fatal bacterial endocarditis developing after urethral dilatation are presented. In 1 patient, the history and physical signs gave ample evidence of rheumatic heart disease; in the other, such evidence was found at autopsy. It is pointed out that chemotherapeutic or antibiotic prophylaxis should be utilized before and after manipulation in such cases.

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MEDICAL PROGRESS

SARCOIDOSIS (Continued)*

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BOSTON

Bone. Localization of the sarcoid lesions in bone has frequently been described, but the true incidence of such involvement is not known. The incidence of roentgenographically demonstrable involvement, however, has ranged between 15 and 25 per cent of cases in several series[5, 38, 49, 131]; in others it has been considerably lower,[45, 132] and only 1 case of such involvement has been reported from Australia.[118] The tendency of the lesions to appear at any time, to last for indefinite periods, to regress spontaneously and even to reappear at a later date[44] makes it necessary to follow cases for an adequate period by means of serial roentgenograms if such localizations are not to be missed. Furthermore, Schaumann[7, 133] has shown that such localizations may occur, and probably often do, without demonstrable roentgenographic or even gross pathologic manifestation, and a reliable estimate is therefore difficult to make even from the autopsied cases.

The radiologically visible bone lesions have a special predilection for the short bones of the hands and feet and, when demonstrable, are of considerable diagnostic significance. A similar appearance, however, has been described in leprosy.[8, 134] Lesions have also been demonstrated in the bones of the carpus and tarsus, in the long bones of the extremities and in the vertebras[69, 135–137]; rarely they are seen throughout the skeleton, including the skull.[40] Histologic examination of such areas reveals diffuse involvement of the bone-marrow spaces, but only lesions that cause destruction of spongy bone or erosion of the compact bone are likely to be visible.[5]

The bone lesions, originally called "ostitis tuberculosa multiplex cystica (or cystoides)," have been described in great detail by Jüngling,[135, 136] Fleischner[137] and many others.[5, 10, 38, 131, 138–140] The roentgenographic appearance takes two main forms: a circumscribed type with characteristic cystoid areas of rarefaction, usually medullary, and with little or no surrounding reactive change; and a diffuse form in which multiple small areas of rarefaction produce a finely reticulated pattern extending over large portions of the bone, often associated with broadening of the shaft and thinning of the cortex.[38] Both types frequently coexist, however, and there may be transitions from one to the other.[5] External manifestations may be seen as fusiform swellings of the fingers or toes, with occasional periarticular subcutaneous nodules or dystrophic nail changes. The swellings are usually symptomless though slight pain may occur in the early stages[38]; lack of pain is probably explained by the fact that periosteum and joints are rarely involved.[5, 9] Occasionally, diffuse, extensive bone destruction causes severe external deformity.

It is difficult to estimate the frequency with which external manifestations are associated with bone lesions. The latter certainly occur in the absence of such manifestations,[5, 9] and in at least one series all 6 cases with bone changes were discovered only by routine roentgenograms of the hands or feet.[47] In Reisner's[38] series, however, all but 1 of 9 cases with visible bone lesions showed external manifestations at the site of involvement. Such manifestations usually mean associated involvement of the skin and subcutaneous tissues of the hands and fingers, and it is of interest that Jüngling[136]

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noted bone lesions in 29 of 30 cases of lupus pernio, which often involves these areas. Reisner notes a high incidence of skin involvement, disseminated as well as local, in cases with bone lesions. Spontaneous regression of bone lesions appears more likely to take place in the diffuse than in the circumscribed form.[38]

Sarcoid lesions have been demonstrated by sternal-marrow biopsy.[141, 142] Dressler[141] also observed some depression of hematopoiesis. Lucia and Aggeler,[143] on the other hand, failed to find granulomas in their biopsies, and the marrow in these areas showed evidence only of mild myelopoietic stimulation as might be seen in any chronic infection.

Skin and mucous membranes. The incidence of skin manifestations, the oldest and best known of the regional localizations, varies widely with the source of material. In the old dermatologic literature, the incidence of skin lesions is very high,[5] but they have been noted in only 40 to 50 per cent of cases in some more recent series[24, 38] and considerably less in others.[47, 96] Many forms have been described, including the miliary and nodular sarcoids of Boeck,[2, 3, 144] the diffuse, plaque-like lupus pernio of Besnier,[13] the rare erythrodermic form of Schaumann,[145] the subcutaneous sarcoid of Darier and Roussy[146, 147] and their variants. All show, on histologic examination, infiltration of the skin with the characteristic granulomas and differ only in the nodularity or diffuseness of the infiltrate, the degree of vascular engorgement and the variable involvement of corium and subcutaneous tissues. They represent, in fact, visible manifestations of the same polymorphism characterizing the roentgenographic pattern in lung and bone, and for this reason, retention of many of the earlier descriptive subtypes has little point. Even the subcutaneous lesions of the "Darier–Roussy" type have been so frequently confused with other conditions, such as erythema induratum and the nodular panniculitis of Weber–Christian, that retention of the term is of little value.[65]

The various skin lesions are described in great detail by various authors[7, 8, 10] and in textbooks of dermatology. The lesions may persist for long periods or may spontaneously regress in the course of a few months. Regression in one area is associated with a new eruption elsewhere in some cases.[38] Healing may leave no residue or may result in an atrophic scar.

Erythema nodosum occasionally occurs as an early skin manifestation.[5, 29, 148–151] Since this condition appears to be a more or less nonspecific manifestation of hypersensitivity and is often seen in association with such diseases as rheumatic fever, tuberculosis and coccidioidomycosis, its occurrence with sarcoidosis is particularly interesting. Furthermore, a pulmonary roentgenographic picture identical with that seen in sarcoidosis occurs in association with erythema nodosum alone,[149, 152, 153] raising the possibility that some common allergic basis underlies at least part of this clearly nonspecific radiologic picture.

Mucous-membrane lesions, essentially similar in character to those in the skin, are described in only 10 to 20 per cent of cases[5, 10, 144, 154] but have probably been frequently overlooked. Involvement of the nasal mucosa may produce a stenosis, and involvement of the larynx may produce hoarseness. Lesions have also been noted in the oral mucosa, pharynx, epiglottis and lower respiratory tract, and on at least two occasions, involvement of the bronchial mucosa has been established by bronchoscopic biopsy.[32, 99]

Eye (lachrymal and salivary glands). Involvement of the eye and its related structures is reported in 25 to 50 per cent of cases in recent series,[24, 38, 42, 47, 155] with incidence figures again varying widely with the sources of the material. These figures are substantially higher than older estimates of 5 to 10 per cent[156, 157] and clearly represent the now general acceptance of the uveoparotid syndrome as a manifestation of sarcoidosis. Ocular localizations have no special temporal relation to other manifestations,[9, 155] but since the attendant discomfort or visual disturbance is more readily noted by the patient than other relatively asymptomatic localizations, they have frequently constituted a presenting complaint.

Eye involvement usually manifests itself as a painless iritis or iridocyclitis, either bilateral or, less commonly, unilateral.[31, 155] It occurs in two forms: a benign serous type, and a more severe nodular variety, which may be associated with corneal involvement. Although the lesions may resorb completely — and this has been described even in large nodules[157] — synechiae, corneal opacities, glaucoma and even phthisis bulbi and loss of sight in one or both eyes have been frequently reported and represent serious complications of the disease.[38, 155] Conjunctival involvement probably occurs in not more than 5 per cent of cases and may not be associated with other ocular lesions.[40, 158, 159] Involvement of the posterior uveal tract is rare,[31, 155] but choroiditis, retinitis, retinal perivasculitis and optic-nerve involvement have been described.[31, 155, 159–162] An occasional complete recovery is reported,[163] but usually the sequelae are serious. Optic-nerve involvement has been associated in most reported cases with involvement of the brain[91, 161, 162] and sometimes with diabetes insipidus.[70]

Uveitis, usually bilateral, may be associated with bilateral enlargement of the parotid gland, and frequently of the submaxillary and submental salivary glands as part of a syndrome that has been termed uveoparotid fever.[47, 92, 151, 164] This complex was first described by Heerfordt[165] in 1909, though similar cases had been reported earlier

and attributed to mumps.[166, 167] Actually, fever occurs in considerably less than half the cases and is usually of low grade, constitutional symptoms are minimal, and evidence of other sarcoid manifestations is noted both clinically and at autopsy.[91–94] Enlargement of the lachrymal glands may be associated, or may occur with salivary-gland enlargement alone as one form of the Mikulicz syndrome.[4, 164, 168, 169] Any of these localizations, however, may develop independently of the others.

Nervous and endocrine systems. Diffuse involvement of the central nervous system has been described on a number of occasions both clinically and at autopsy.[89, 164, 170, 171] Lethargy simulating that of encephalitis lethargica may occur and has cleared up with improvement of other manifestations.[164] Evidence of peripheral-nerve affection may be noted in the form of pareses and paresthesias or loss of deep reflexes. Such findings are rare, however, and may be due to spinal-cord involvement; they constitute a point of differentiation from tuberculoid leprosy in which peripheral-nerve invasion is common.[172] Involvement of the cranial nerves, frequently transient, may also occur, often in association with the uveoparotid syndrome. The facial nerve is most commonly affected, and the resultant palsy is usually of the peripheral type. It tends to follow enlargement of the parotid gland, though occasionally it precedes it and may even be an initial symptom.[173] Involvements of the auditory, glossopharyngeal and oculomotor nerves may also occur, with resultant deafness, palatal paralysis and varying degrees of cycloplegia.[48, 92, 164, 165, 174] A case of Adie's syndrome with tonic pupils and absent tendon reflexes has been attributed to sarcoidosis.[175] The hypoglossal nerve has been affected on at least one occasion.[176] Dysarthria and dysphagia have also been noted but may at times be due to marked dryness of the mouth resulting from salivary-gland involvement.[163]

Localization in the hypothalamic region and pituitary gland may be associated with the syndrome of diabetes insipidus, and such localizations have on several occasions been confirmed at autopsy.[24, 40, 70, 177] This has not been invariable, however.[38] A number of these cases have also been associated with salivary-gland involvement, and in the presence of thirst due to dryness of the mouth, symptoms of polydipsia and polyuria, like dysarthria and dysphagia, must be evaluated with caution.

Other stigmas of pituitary-gland involvement have occasionally been noted. Kraus[71] has described a case in which polyuria, genital dystrophy, cessation of menses and hypertrichosis were associated with involvement of the pituitary gland and its stalk, but this case was unfortunately complicated by a chromophobe adenoma. In another case with panhypopituitarism, the granuloma in the pituitary gland may well have been a tuberculoma.[178]

Lesions have been observed in the testis and epididymis,[24, 80, 94, 179] prostate,[24] and thyroid gland[94, 100] usually without disturbance. Hyperthyroidism in the presence of demonstrable sarcoid lesions in the thyroid gland has been described,[180] but a causal relation seems unlikely. In contradistinction to caseating tuberculosis, involvement of the adrenal glands appears to be quite rare.

Gastrointestinal and isolated sarcoid manifestations. Involvement of the stomach and intestines is recorded very infrequently in association with generalized sarcoidosis. Occasionally, however, localized lesions have occurred in the stomach,[181] small intestine, appendix and colon,[29, 182–185] and in the regional lymph nodes draining such areas in the absence of manifestations elsewhere.

The occurrence of epithelioid and giant cells in some cases of regional enteritis has raised the possibility that the two diseases are related. In occasional cases these granulomas are clearly of sarcoid type to the point of massive formation of noncaseating tubercles without evidence of tubercle bacilli even on animal inoculation,[186] but, with one possible exception,[187] such sarcoid lesions have been strictly isolated manifestations. In most cases the scattered granulomas seen in the bowel wall in regional enteritis bear only a superficial resemblance to the lesions of sarcoidosis. They tend to be small, widely scattered, rather indistinct collections of histiocytes and epithelioid cells, often containing one or two giant cells, and most authors have been content to attribute such findings to foreign-body reaction.[188] In at least one case surgical removal of the affected bowel revealed no sarcoid lesions, although evidence of disseminated sarcoidosis existed elsewhere.[189] It seems highly unlikely, therefore, that any considerable number of cases of regional enteritis belong in the sarcoid group.[40, 190]

Isolated sarcoid lesions have also been described in various lymph-node groups, the skin, the spleen and other organs. Occasionally, these findings represent temporary localized phases of the disease stabilized in the process of progression or regression. In most cases, however, a diagnosis of generalized sarcoidosis is totally unwarranted. As pointed out below in the discussion of etiology, a large number of bacterial and chemical agents seem capable of reproducing the histologic features of sarcoidosis. For this reason it seems wise to distinguish the *sarcoid lesion* as a descriptive histologic term from *sarcoidosis*, a disseminated disease associated with such lesions.[191]

Miscellaneous manifestations. Occasional localizations have been described in the pancreas,[80] breast[4, 38, 109] and skeletal muscle.[10, 42, 142] The

serous membranes are infrequently involved, though pleural or pericardial effusion is occasionally seen.[47]

A wide variety of conditions has been described in association with sarcoidosis including Hodgkin's disease,[43] hemolytic anemia[47, 192] and polyarthritis,[142, 193] but coexistence in most of these cases does not necessarily imply causal relation. On the other hand, thrombocytopenic purpura has been recorded with sufficient frequency to be significant,[29, 71, 194–196] and the same observation applies to such an associated syndrome as diabetes insipidus.

Blood. The white-cell count tends to be within normal limits or low in the large majority of cases, and definite leukopenia has been recorded in a third to a half of the cases in some series.[9, 38] The differential count often shows a mild monocytosis, occasionally as high as 15 per cent, but this is not constant and may even vary from time to time in the same case.[42] However, if monocytosis is accepted as a manifestation in the circulating blood of the reticuloendothelial activity giving rise to epithelioid granulomas, this finding might be expected to occur only during the active phases of the disease if it occurs at all.[4, 23] Mild eosinophilia (counts rarely over 10 to 15, but occasionally as high as 35 per cent[24]) is another inconstant finding; it has been noted in a fourth to a half of the cases in some series.[24, 25, 38]

Changes in the red-cell count or hemoglobin are of little significance. There may be a mild anemia, or polycythemia may occur in association with pulmonary fibrosis.[4] The sedimentation rate is frequently increased,[24, 42, 47] and this has been observed not only in patients in the active phases of the disease[24, 42] but also in patients whose lesions appear well stabilized.[38]

Elevation of the total serum protein, a fact to which Salvesen[124] first called attention in 1935, has since been noted in many cases. The rise may be considerable so that the value may exceed 9.0 gm. per 100 cc., and is exclusively in the globulin fraction. The rise in globulin may occur at the expense of the albumin so that reversals of the ratio may be observed even in cases in which the total protein shows little or no increase.[24, 38] Again, these changes are inconstant and, when present, are usually associated with an active phase of the disease; in the healed phases the total protein and albumin-globulin ratio tend to be normal.[41, 42, 197] Electrophoretic studies on the serum proteins have shown that the rise is primarily in the gamma-globulin fraction.[197, 198] The findings are consistent with those seen in other chronic infections, such as lymphogranuloma inguinale and kala azar, and have suggested antibody formation to several investigators.[198, 199] Although Harrell[42, 200] has reported a substance resembling Bence–Jones protein in the urine in 2 cases, it has been shown that the proteins in multiple myeloma present a different electrophoretic pattern.[199]

Elevations in serum calcium, with values as high as 16.5 mg. per 100 cc., have also been noted. The hypercalcemia has, on rare occasions, been associated with renal calculi,[29, 130] renal insufficiency[127] and even diffuse metastatic calcification.[128] Hypercalcemia, when it occurs, is often associated with hyperglobulinemia, and some relation between the two has been suggested on the basis of the calcium-binding power of serum protein. The calcium level does not vary in proportion with the protein, however, and may be higher than can be accounted for by the globulin elevation.[34, 200] Furthermore, most of the serum calcium is bound to the albumin fraction, with the globulin increment in hyperglobulinemia binding very little calcium.[201, 202] This suggests that the calcium increment in these cases is in an unbound state and, as such, independent of the hyperproteinemia except so far as each is a manifestation of disease activity. In the inactive phase, the calcium, like the protein, returns to normal levels. The relation of calcium levels to bone involvement is not certain. Hypercalcemia has been noted in both the presence and the absence of roentgenographically demonstrable bone lesions, but it is known that bone involvement may occur in the absence of roentgenographic changes.[7, 139]

In spite of the elevated calcium, serum phosphorus tends to be normal or at most very slightly elevated; the low phosphorus values observed in hyperparathyroidism are not seen. Moderate elevations in the serum alkaline phosphatase have been recorded, but the phosphatase values cannot be correlated with the extent or activity of the bone lesions or with the calcium content of the blood.[200] Cholesterol values in the neighborhood of 130 mg. per 100 cc. have occasionally been noted.[24] In the absence of renal insufficiency, nonprotein nitrogen values are within normal limits.

The various serologic reactions that have been reported have been noncontributory. Serologic reactions for syphilis have been positive in some cases; Gravesen[5] reports only 13 positive findings among 433 patients in the literature so tested, but this figure seems rather low. In this country a higher incidence has been noted, probably owing in part to the high proportion of Negroes in the various series. In several cases positive blood Wassermann reactions have been inconstant, or have persisted in spite of intensive antisyphilitic therapy, suggesting the possibility that some reactions are nonspecific.[38, 164]

Tuberculin reaction. The high incidence of sarcoid patients who either fail to react to tuberculin or react weakly to concentrations as high as 1.0 mg. or more is a fact upon which practically all authors are agreed. Most estimates of the incidence of such nonreactors range between 60 and 70 per cent of cases, the remaining positive reactions

usually tending to be weak.[8, 10, 203] In Reisner's[38] series, 60 per cent of patients failed to react to doses as high as 1.0 mg., and 10 of these tested with 10.0 mg. also failed to react. These figures are significantly higher than the expected incidence of nonreactors in an urban population such as the one from which this series was drawn. Unfortunately, however, the majority of reported cases were inadequately tested in the higher and more significant concentrations, and few of the autopsied cases have had an adequate work-up in this regard. Focal reactions to tuberculin have also been negative in such cases.[59]

Kveim reaction. Intradermal injection of extracts of sarcoid tissue have produced characteristic skin reactions in a number of patients with sarcoidosis.[204–208] The antigen, prepared after the manner of the Frei antigen for lymphogranuloma inguinale, is extremely thermostable[206–208] and seems to be ineffectual unless injected with a large-bore needle in grossly particulate form.[208] The typical reaction, in the form of an indurated and later crusted, occasionally necrotic papule, is slow to evolve, often requiring weeks to reach maximum size and persisting for many months; histologic examination of the sites of the positive tests reveals a granulomatous structure entirely consistent with that of spontaneous sarcoid lesions in the skin. Evanescent early responses, first described by Williams and Nickerson,[209] are apparently nonspecific.[206]

The incidence of positive reactions in different series varies. Danbolt and Nilssen[205] produced a positive reaction in 34 of 36 patients tested. Putkonen[206] found the test positive in 33 of 42 patients, and such cases were practically always in an active phase, with lesions demonstrable in the skin, lymph nodes or tonsils; the test was almost always negative when the lesions had healed. Nelson,[208] testing a series of 17 American Negroes with sarcoidosis, produced characteristic reactions in 7 of 11 active cases, whereas the reactions in 6 inactive cases remained negative. Tests in apparently normal controls have been entirely negative or of low order, and negative tests have also been obtained in patients with a variety of skin lesions including leprosy, tuberculosis and lymphogranuloma inguinale.[206]

The typical Kveim reaction, therefore, seems to be rather specific for cases of sarcoidosis, particularly cases with demonstrable activity. The antigen itself, however, is far less specific. Nelson[208] was able to produce identical reactions both clinically and histologically, and in the same patients, using antigens prepared from various sarcoid lesions and from normal human spleen. Similar reactions have also been produced with antigens prepared from the lesions of lymphatic leukemia.[206–208] The histologically characteristic lesions produced in some sarcoid patients with living BCG,[210, 211] living[212] or heat-killed[213] human tubercle bacilli and even nonspecific substances such as India ink[214] may well be of a similar nature, and such reactions may also explain the appearance of subcutaneous granulomas following exposure to beryllium compounds and other substances in apparently normal persons. The findings to date suggest an obvious parallel with the history of the Wassermann antigen.

As a diagnostic test, the Kveim reaction is markedly limited by the slow evolution, long duration and occasional severity of the lesions produced. The test also sheds little light on the etiology of the disease but offers a challenging approach to the problem of the pathogenesis of sarcoid lesions.

Course and Prognosis

Sarcoidosis tends to run a prolonged, low-grade, chronic and unpredictable course, ranging in duration from several months to many years. Occasionally, the onset is abrupt and febrile, and a case has been reported in which such an acute onset occurred thirty-six hours after childbirth.[215] Often, however, it is exceedingly difficult to determine the exact time of onset so that estimates of average duration are not too reliable; these have varied in different series from two and two-tenths[30] to eight or more years.[5] In some series individual cases have been followed for fifteen years or more.[38, 41] Residual lesions were found at autopsy in 1 of Boeck's early cases twenty-nine years after the original diagnosis had been made,[84] and another case was followed clinically for thirty-four years.[216] The benignity of the course and the generally good prognosis have been repeatedly stressed, and it is certain that a considerable number of patients recover completely. In a group of 37 cases with adequate follow-up study reported by King,[30] half of which were confirmed by biopsy, 23 cleared completely or almost completely within three years, 8 showed no change in periods up to four years, and the remaining 3 showed extension. On the other hand, in a series of 28 cases followed by Reisner[38] for an average period of five years, all confirmed by biopsy, regression of lesions to the point of disappearance occurred in only a third. In an additional third the disease was essentially stationary or consisted of alternate periods of progression and regression, and in the final third the disease was progressive to the point of death in 7 cases. In Thomas's[44] series of 15 cases, the results were approximately the same. It is possible that a great many of the published cases have been followed for an insufficient period so that the general excellence of the outlook may have been overemphasized. The high incidence of Negroes in the series of Reisner[38] and Thomas[44] (86 and 80 per cent respectively) may also have had some bearing on the course of these cases, and sarcoidosis in the Negro may, in fact, represent a special problem.[217]

Death, when it occurs, is usually due to pulmonary fibrosis, with resultant respiratory and cardiac insufficiency, or to superimposed caseating tuberculosis. Extensive localizations in vital areas such as the heart, and perhaps the kidney and brain, may also be fatal in some cases. Other serious complications include glaucoma and phthisis bulbi resulting from ocular involvement, and the occasional mutilating effects of bone and skin lesions.

Treatment

The evaluation of therapeutic measures has been enormously complicated by the marked tendency of the disease to regress spontaneously. A wide variety of agents, including salts of gold and arsenic, chaulmoogra oil, antileprol and others far too numerous to mention, have been tried with equivocal results. Simple measures such as fresh air, sunlight, good diet and rest have been equally satisfactory if not more so.

X-ray therapy has been tried with beneficial effects in a few cases,[43, 82, 218] and little or no effect in others.[47] More recently, the successful use of calciferol in the treatment of lupus vulgaris has suggested its use in sarcoidosis as well. Curtis and his coworkers[176] report considerable improvement following the use of large doses of both calciferol and dihydrotachysterol. Toxic reactions were present in all cases, however, though no recognized permanent damage was noted, and Lomholt[219] believes that patients with sarcoidosis tolerate calciferol less well than those with lupus.

Etiologic Aspects

At some time or other practically every agent capable of producing a granulomatous reaction or of diffusely affecting the reticuloendothelial system has been suggested as a possible cause of sarcoidosis. The arguments usually consist in accenting similarities between sarcoidosis and the known disease produced by such agents, at the same time ignoring or minimizing differences. The greater part of the discussion has centered about the possible etiologic role of the tubercle bacillus, most authors since the time of Boeck going on record either for or against. The repeated failures, except on a very few occasions, to identify this organism in the lesions either microscopically or by animal inoculation, as well as the high incidence of weak reactors or nonreactors to tuberculin in the group, have provided the greatest stumbling block to the general acceptance of this theory — though, paradoxically enough, both sides use these findings as their strongest arguments.

Tuberculosis

The case for tuberculosis has been presented in detail by Pinner[4, 191] whose arguments are essentially those of the many other proponents of this theory. The arguments, both factual and theoretical, that have been mustered on both sides of the question can be conveniently grouped into four categories: bacteriologic, anatomic, immunologic and epidemiologic.

Bacteriologic arguments. The identification of acid-fast bacilli in sarcoid lesions has been sporadically reported since the time of Boeck.[3] The various positive findings have been listed by Pinner[4] and others,[10, 25] and several more have been reported since.[168, 195, 220] However, these represent only a minute fraction of cases in which such organisms have not been found, often after exhaustive microscopical search and inoculation into a wide variety of animals.

Attempts to explain this phenomenon on the ground that the organisms are in a filterable form, or have dissociated into nonacid-fast or partially acid-fast forms, are highly theoretical and unconvincing.[102, 220, 221] On the other hand, if the lesions are actually due to the usual form of the tubercle bacillus, it is necessary to assume that the organisms are quickly killed and disintegrated at their points of focalization under the influence of the local immune forces. Under these circumstances, the lipids of the bacillus might be capable of inducing tubercle formation, as has been demonstrated experimentally,[77, 78] whereas the proteins of the bacillus, in the absence of hypersensitivity, produce no significant necrosis or constitutional reaction. Thus, the same immunologic situation responsible for the prompt killing of the bacilli might explain the morphologic character of the lesion.[4, 120, 222]

If this is true, organisms might be expected to be identified only in very early lesions. Kyrle,[223] in a frequently quoted and controversial case, reported a series of biopsies on a very early skin lesion. Abundant tubercle bacilli were seen on the tenth day, together with a nonspecific infiltration of lymphocytes and histiocytes, but a guinea-pig inoculation was negative. By the twenty-first day, the infiltrate was composed largely of epithelioid cells with some giant cells, and the bacilli were much reduced in number; guinea-pig inoculation was again negative. By the thirty-sixth day, the epithelioid-cell foci were free of organisms, contained numerous giant cells and were being encapsulated by fibrous tissue. By the ninety-fourth day, the infiltrate had disappeared. One of two guinea pigs inoculated with blood from the patient during a febrile episode developed tuberculosis. This case is exceedingly difficult to evaluate since it is both unique and atypical.

There is plenty of experimental evidence that acquired resistance to tuberculosis can increase the ability of the body to destroy tubercle bacilli, and the decrease in organisms may be sufficiently marked to render it very difficult to find them even on serial section.[224] It is also known that bacilli may be impossible to find in many primary foci and

even in some postprimary disseminated lesions.[120] Whether the organisms are capable of being killed and so completely altered or removed from practically all the lesions that microscopical search and animal inoculations are negative in the great majority of cases is another matter, however; this point has still to be proved, especially since it has been demonstrated that even killed organisms may persist in tissues for some time, retaining recognizable shape and staining qualities.[225]

Several investigators have been attempting to produce specific lesions in sarcoid patients by the use of tubercle bacilli or their products. Positive results have been obtained in some cases with BCG[210, 211] and living or heat-killed tubercle bacilli,[212, 213] but the results are inconstant.[226] As noted above, similar responses can be produced by extracts of sarcoid tissue or even leukemic tissue and normal spleen (Kveim antigens). An attempt to invoke characteristic lesions in sarcoid patients with tuberculophosphatide has been unsuccessful.[227]

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 34451

PRESENTATION OF CASE

A forty-one-year-old carpenter entered the hospital because of fever and delirium.

The patient had been well and active until two days before admission, when he developed a slight cough, a feeling of tightness in the chest and a mild headache. The next day he refused his breakfast but reported for work only to return home shortly, complaining of cough and headache. He went to bed with a shaking chill and a temperature of 103.5°F. Sixteen grams of sulfadiazine was prescribed and taken in divided doses during the next twenty-four hours. Despite this he grew gradually less responsive and became delirious, with continuance of the high fever. He was then given 300,000 units of penicillin in oil and sent to the hospital.

The past history revealed an episode several years previously of ankle pains, which were severe enough to cause him to stay in bed a month. A few years later he was told that he had a heart murmur. He had had frequent colds and a chronic, nonproductive cough. Since his father's death from cardiac disease five months previously, he had been considerably concerned about heart disease and began to complain of pain in the anterior chest and mild exertional dyspnea although there was no orthopnea, ankle edema or palpitation.

Physical examination showed a well developed, obese man who was semistuporous, warm, flushed and sweating. There were a few questionable petechiae on the arms, neck and buccal mucosa, and small, blotchy, pink macules on the trunk and legs. The eyes were not remarkable although the fundi were not seen. The throat was slightly injected. The ears were normal. The neck was supple, and there was no venous distention. The heart was enlarged, the border of cardiac dullness extending 2 cm. beyond the midclavicular line. There was tachycardia with frequent extrasystoles. There was a Grade II, rumbling, diastolic, apical

murmur heard only in the left lateral decubitus position. The aortic second sound was equal to the pulmonic. The lungs were clear, except for a few crackles at the left base posteriorly. The abdomen was normal. Neurologic examination was negative.

The temperature was 104°F., the pulse 112, and the respirations 28. The blood pressure was 110 systolic, 70 diastolic.

Laboratory studies showed a urine with a specific gravity of 1.018, a + test for albumin, but no sugar or bile; the sediment contained 2 or 3 white cells and 2 or 3 red cells per high-power field. There were no casts. The hemoglobin was 16 gm., and the white-cell count was 13,300, with 83 per cent neutrophils. A stool was guaiac negative. The nonprotein nitrogen was 37 mg. and the total protein 6 gm. per 100 cc. Six flasks were inoculated with blood, and all grew coagulase-positive *Staphylococcus aureus*. A spinal tap was attempted, but only blood was obtained.

The patient was placed on penicillin, 2,000,000 units a day, digitalized with purodigin and given 75 mg. of heparin. On this regime the blood cultures became sterile on the fifth hospital day and remained so. The temperature gradually subsided from daily levels of 103 to 104°F. to 99 to 101°F. in the course of two weeks. Despite these improvements he remained drowsy, had occasional bouts of hiccuping, but complained only of poor appetite. Approximately two weeks after admission the nonprotein nitrogen was found to be 160 mg. per 100 cc. Additional laboratory studies showed the urinary specific gravity to be 1.008, with a ++ test for albumin and rare white cells and red cells in the sediment. The urine culture showed *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*). The blood sodium was 123.4 milliequiv., the chloride 90 milliequiv., and the carbon dioxide 25.8 milliequiv. per liter, and the calcium was 8.7 mg. and the phosphorus 6.4 mg. per 100 cc. The blood pressure was 190 systolic, 110 diastolic. Repeated blood cultures were negative. Four days later rapid breathing, increase in the pulse to 140 and moist rales in the lungs suddenly developed, clearing rapidly with morphine and tourniquets. In spite of therapy he showed little improvement in his general condition, and the urinary output, which had been maintained at 1500 to 2000 cc. a day, dropped sharply to less than 500 cc. a day, averaging about 350 cc. The urine specific gravity was 1.005. There was a ++++ test for albumin and many white cells and rare red cells in the sediment. The white-cell count rose to 22,000, with 86 per cent neutrophils, 9 per cent lymphocytes and 5 per cent eosinophils.

The course was steadily downhill, and approximately one month after admission the lungs suddenly became filled with bubbling rales, and the patient became sweaty and apprehensive. The blood pressure was 210 systolic, 130 diastolic, the pulse 160, and the respirations 10. He failed to rally and expired soon after the onset of this episode.

Differential Diagnosis

Dr. Alfred Kranes: May we know when this diminution in the urinary output took place? It is not quite clear from the record. I wondered whether the nonprotein nitrogen rose in the presence of a normal urinary output during the first weeks, and with a normal specific gravity.

Dr. Rita M. Kelley: The nonprotein nitrogen rose while the output was still adequate, but the specific gravity became low; only in the last few days was the output poor. The nonprotein nitrogen rose steadily and was elevated for about ten days before death.

Dr. Kranes: The nonprotein nitrogen began to rise at the end of two weeks, but the patient lived a month.

Dr. Kelley: That is right, but the decrease in output came only a few days before death.

Dr. Kranes: Therefore, it rose in spite of a normal urine output, with a low specific gravity. Might I ask whether the specific gravity rose?

Dr. Kelley: It never rose.

Dr. Kranes: We are faced with a man who came in with an acute fulminating *Staph. aureus* septicemia, which was promptly recognized and treated, and who died one month later, with one of the complications of renal insufficiency — namely, acute pulmonary edema.

As I see the problem, we are asked to try to guess what was the trouble with the kidneys. So far as the acute episode that brought him in is concerned, the record is fairly clear-cut, although exactly what the portal of entry for the staphylococcus was is not at all clear. Very often we do not know just how invasion took place. In this case, since the man was a carpenter, he may have had what seemed to be an insignificant skin infection, and from that, very virulent organisms entered the blood stream, producing the picture described. He may have had an acute sinusitis or ethmoiditis. I do not see how we can possibly guess the origin of the septicemia. Whether or not he had a bacterial endocarditis is also a guess. He probably did, although not primary. The chances that the organisms landed on one of the heart valves are certainly fairly great in this particular case, in which we have reason to believe mitral rheumatic heart disease existed, probably mitral stenosis. There is a fairly good probability that he had an acute bacterial vegetation engrafted on the mitral and possibly on some of the other valves. Do we know any more about the murmur?

Dr. Kelley: The mitral diastolic murmur remained the same. There were no new murmurs.

Dr. Kranes: Presumably mitral stenosis and possibly acute bacterial endocarditis.

Were there any x-ray films, and are they helpful at all?

DR. JOSEPH HANELIN: The patient was too ill to have conventional films. The films were obtained with the patient recumbent, this being an anteroposterior instead of the usual posteroanterior projection. The heart is large. Despite the magnification it looks larger than one would expect to see it in this position. There is a density superimposed on the right side of the heart, which may represent an enlarged left auricle. The lung fields are probably clear, and these little circular densities throughout the lung probably represent vascular shadows rather than metastatic abscesses. The spleen is perhaps just visible — if that is the spleen, it does not appear enlarged. The bone structures are normal.

DR. KRANES: When, during the course of the illness, was this film taken?

DR. KELLEY: On admission.

DR. KRANES: In the days before intensive chemotherapy, the patient probably would have died within a few days or a week after admission, and the chances are that at autopsy many metastatic abscesses would have been found in various parts of the body, most commonly in the kidneys, brain and myocardium — the sites most commonly affected. Whether, despite the intensity of treatment, residual abscesses remained is impossible to say on the evidence. There is no evidence of myocardial involvement except for two attacks of acute pulmonary edema. There was certainly no evidence of cardiac tamponade. The patient ran a temperature of 101°F. in the hospital, so presumably the infection may not have been completely healed.

The real problem is not so much the bacterial infection as the nature of the renal lesion. Time was when in a case of this sort we would be satisfied to make a diagnosis of acute nephritis and let it go at that, but nowadays we are expected to try to predict what the microscopical lesion will be. I find that quite impossible, but I see no reason why we should not look over the possibilities. In this particular case there were many factors operating that may have produced renal damage. In many cases of kidney disease we are hard put to find the cause. There are many possible causes here. The first and most obvious one is the large dose of sulfadiazine that he received on the day before admission — 16 gm. in twenty-four hours. One wonders what role sulfonamides played in the production of this picture. As you know, sulfonamides may produce renal damage in any one of four ways. They can plug up the tubules; they can produce a lower-nephron nephrosis; they can cause an acute interstitial nephritis involving neither the tubules nor the glomeruli; and they can produce acute necrotizing arterial lesions similar to those found in periarteritis nodosa. These were first described by Rich* several years ago, and since then isolated case reports have appeared in which periarteritis-like lesions are found following sulfonamide administration, the patients frequently dying in uremia. Which one of these may have been operating in this case I find it difficult to say. I think we can rule out the first one — that is, plugging of the tubules, since there was no anuria. Lower-nephron nephrosis, also, usually leads to striking oliguria or anuria, which this patient did not have. I think it would be unusual for a person with lower-nephron nephrosis to have an adequate urinary output for so long and to develop azotemia. The other two types I cannot rule out. It is conceivable that he had a periarterial lesion or interstitial nephritis due to sulfonamide. As for acute glomerulonephritis, one would expect a good deal more hematuria than described here. I think we must assume that this patient did have an acute lesion, since there is no evidence that the kidneys had previously been involved in any way. On the law of chances I think that glomerulonephritis is very unlikely.

One naturally wonders whether the kidney disease could possibly be linked to the primary illness. Can the staphylococcus be incriminated in this case? As I said before, in the prepenicillin and presulfonamide era this patient would have died in several days with evidence of septic emboli in the kidneys, either several discrete abscesses or miliary abscesses of the cortexes. As I read this, I wondered to myself, although I have never seen it described, whether if such a patient were kept alive with chemotherapy and the septic element controlled, he might live long enough to develop renal insufficiency from these lesions. I have never heard of it, but I think it is not improbable. One might find diffuse miliary abscesses throughout the cortexes of the kidney interfering with renal function. We are dealing here with a virulent organism that was coagulase positive and may not have been reached by penicillin.

While on the subject of the staphylococcus, I suppose it is not too far-fetched to bring up one other possibility, although again I hesitate to mention it because of its rarity. That is bilateral cortical necrosis. These cases are described chiefly in women, the majority of them occurring after delivery. A few cases have been described in men, however. The reason I mention it here is that lesions like bilateral cortical necrosis have been produced experimentally in animals by the injection of staphylococcus toxin. Since this patient suffered from a severe staphylococcal septicemia, one wonders if it could possibly have been a source for the renal lesion.

I have no way of choosing among these various possibilities. I am forced to make a guess. On the law of probabilities I should think that sulfonamides

*Rich, A. R. Role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.* **71**:123-140, 1942.

would be the most likely etiology, although there are certain aspects of the picture that are atypical. The other possibilities that I have mentioned cannot be ruled out.

DR. MERRILL SOSMAN: Was the brain removed at autopsy, Dr. Mallory?

DR. TRACY B. MALLORY: No.

DR. SOSMAN: Then there is no use speculating about that. I might ask Dr. Kranes what he expects to find in the heart — whether or not it will be an acute bacterial endocarditis.

DR. KRANES: An enlarged heart with rheumatic mitral disease and probably some acute bacterial vegetations containing *Staph. aureus*.

DR. SOSMAN: Do you think that the renal lesions could have been embolic?

DR. KRANES: You mean the type of embolic glomerulonephritis found with *Streptococcus viridans*? There is no evidence in this case that *S. viridans* was found. I hesitate to make a diagnosis of two organisms when only one is presented to me.

DR. MALLORY: Will you tell us about the impressions of the clinicians on the ward, Dr. Kelley?

DR. KELLEY: Most of us thought that it was probably an acute nephritis. We did not know the amount of sulfonamide administered until later when the patient's physician came in. At that point we inclined to acute diffuse nephritis on the basis of the maintenance of the penicillin blood level, ten times the sensitivity of the organism. We believed that the infecting organism had been controlled by the penicillin.

DR. MALLORY: How did you explain the fever?

DR. KELLEY: He also had a slightly infected urine because he was maintained on constant catheterization since he was unable to void spontaneously.

DR. JOHN B. QUINBY: Are the urinary findings, the first ones, adequate to rule out the thought of a pre-existing element of renal failure based on old pyelonephritis?

DR. KRANES: No; that is always possible in a perfectly healthy man. One must remember that a patient can have renal disease and maintain excellent health. I think it is possible but not probable.

CLINICAL DIAGNOSES

Acute glomerulonephritis.
Acute pulmonary edema.
Acute bacterial endocarditis.
Rheumatic heart disease.
Cystitis.

DR. KRANES'S DIAGNOSES

Rheumatic heart disease.
Staph. aureus septicemia.
Acute bacterial endocarditis.
Acute nephritis, cause ? sulfonamide nephritis.

ANATOMICAL DIAGNOSES

Endocarditis, acute bacterial (Staph. aureus), *mitral and aortic valves, healing.*
Endocarditis, rheumatic, old, mitral and aortic valves.
Glomerulonephritis, acute.
Arteriosclerosis, coronary, severe; aortic, mild.
Myocardial infarct, old.
Infarcts, recent, kidney and spleen.
Cystitis, acute hemorrhagic.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy showed a very much enlarged heart, weighing over 500 gm., with evidence of old rheumatic damage to both mitral and aortic valves. The mitral valve had, in addition, a very large, friable vegetation, measuring nearly 3 cm. in diameter, and there were a few, very small, acute vegetations on the aortic valve. There was a large area of scarring in the myocardium, and on examining the coronary arteries we found that they were reduced to almost pinpoint lumens. So we had two possible sources for the myocardial scars: emboli from the acute endocarditis and coronary sclerosis. The microscopical sections suggest that both played a part. A portion of the scarring was very old, obviously many months if not several years in age — completely healed, fibrous scars with no trace of the necrotic muscle cells. In fact, there was slight replacement of the scar by adipose tissue. These scars must have long antedated the endocarditis, and I ascribe them to the coronary-artery disease. There were also, however, many small foci of acute myocardial necrosis scattered throughout the heart, which I think were undoubtedly due to emboli. The kidneys were the major point of interest. They were extremely enlarged, with very thick, pale cortexes, and showed typical acute diffuse glomerulonephritis. There were infarcts in the spleen and in one of the kidneys, evidently secondary to the endocarditis, and a very severe terminal pulmonary edema with old, calcified scars in the pleura near the base, the etiology of which I am uncertain about, but they were probably tuberculous.

Glomerular lesions can occur in the ordinary type of *S. viridans* endocarditis in two forms: involvement of scattered glomeruli or of portions of individual glomeruli, which is ordinarily called embolic glomerulonephritis. That is the common type and does not usually lead to renal insufficiency, although generally associated with red cells in the urine. In about 10 per cent of endocarditis cases a diffuse glomerulonephritis develops. I think that this is the first case of diffuse glomerulonephritis that I can remember in which the nephritis was associated with staphylococcal rather than strepto-

coccal infection. There can be no doubt about the organism, however. It was grown repeatedly.

DR. KRANES: How about the absence of hematuria? Or was there hematuria in this case? Is that not a bit unusual?

DR. MALLORY: There may have been more than was apparent in the record.

DR. KELLEY: No; there was never very much.

CASE 34452

PRESENTATION OF CASE

A sixty-nine-year-old woman was admitted to the hospital because of abdominal distention and lower suprapubic pain.

Thirty-eight years before admission a hysterectomy had been performed because of fibroids. Ten years before admission during a routine physical checkup, including x-ray examination, a nonfunctioning gall bladder was discovered. The patient at this time admitted an intolerance to fried and fatty foods of thirty years' duration. Eight months before admission the patient was awakened in the early morning by a sharp, excruciating, right-upper-quadrant pain, which radiated to the scapula. The acute episode passed off after several hours, leaving residual soreness. There was no associated nausea or vomiting, dark urine, acholic stools, jaundice or chills and fever. During the six weeks that followed she had several recurrent attacks of right-upper-quadrant pain. Five months before admission she noted failing appetite, loss of weight, weakness and lethargy. Two months before admission she became jaundiced and complained of itching. She could not report on the color of stools and urine. Chills and fever were absent. She did have daily nausea and vomiting until admission. The weight loss by now had amounted to 24 pounds. Two weeks before admission it was discovered that the blood sugar was 390 mg. per 100 cc., whereas the value had been normal two weeks before. The jaundice subsided in the four weeks preceding admission. During the two weeks before admission the patient complained of epigastric pain radiating through to the back and she noticed a lump in the neck. Twenty-four hours before admission an enema was given because she had had no bowel movement for twenty-four hours. The enema was not expelled, and she suddenly became distended and complained of lower abdominal, suprapubic pain. The vomiting continued without change. At the time of admission she had passed no gas by rectum.

Physical examination showed a left supraclavicular lymph node that was enlarged, firm and freely movable. The heart was not enlarged, and there was a Grade II systolic murmur at the apex transmitted to all areas. The abdomen was distended and diffusely tender. No peristalsis was heard except during the patient's rare paroxysms of pain, when a few scattered, high-pitched sounds were audible. On pelvic and rectal examination there was a large, retained cervix, which could not be visualized. There was a very tender mass in the cul-de-sac, which felt lobulated. This mass was continuous with the cervix, motion of which caused severe pain. There was a small amount of soft feces in the rectum that was guaiac positive. The white-cell count was 24,000.

The temperature was 97°F., the pulse 90, and the respirations 20. The blood pressure was 118 systolic, 70 diastolic.

Shortly after admission the patient rapidly went into shock, the blood pressure was unobtainable, and the pulse was 140. Distention and generalized tenderness were increased. Rigidity and rebound tenderness were present. The temperature at this time was 101°F. In spite of blood transfusion the patient never recovered from shock, and the temperature reached 107°F. terminally. She died thirty hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD H. SWEET: This woman had a long history of encounters with the medical profession. The hysterectomy done thirty-eight years before admission undoubtedly was a supravaginal hysterectomy, leaving the cervix.

The episode eight months before admission is rather characteristic of gallstone colic. It is very frequent for a patient to have gallstone colic in the absence of nausea and vomiting. If infection is absent, one need not see changes in the temperature, pulse and white-cell count. If the stone does not pass through the cystic duct, there is, of course, no jaundice. One can relate all these symptoms to gall-bladder disease except the lump in the neck. She could have had, to explain the later difficulties, increasing trouble with the gall bladder, a mild or moderate degree of infection and passage of the stone into the duct, with jaundice and all the characteristic signs of obstruction — perhaps subsequent release of the obstruction because of passage of the stones into the intestinal tract.

I do not know why she developed a high blood sugar. There is nothing else to suggest that she had pancreatitis, although she complained of pain radiating to the back, which might go with it.

How can the lump in the neck be connected with gall-bladder disease? It may have been a metastasis from carcinoma of the gall bladder. Anyone who has had gallstones for a period of many years is likely to develop a carcinoma. Conversely I at least have never seen a carcinoma of the gall bladder develop in the absence of stones, although it may, of course, be found. The lump in the neck, which developed out of a clear sky, is an important finding. Of course one should not place too much emphasis on the wording of these histories, but if

this patient became distended very promptly as soon as the enema was given, it might mean that the enema fluid escaped from the colon into the peritoneal cavity, especially if the distention was attended by sudden, severe, abdominal pain. On the other hand, perforation of the colon is rare as a result of enemas. It is a very unusual occurrence in my experience, with the exception of instrumental perforations, which occur while a colostomy is being irrigated or something of that sort or in the presence of a lesion in the wall of the colon itself. Carcinomas of the colon rarely perforate. On the other hand, perforation of the colon, proximal to an obstructing carcinoma, is not infrequent. We have seen such things occur with an overdistended colon when a perforation of the cecum may occur as a result sometimes of an enema given in the X-Ray Department. Lymphomas sometimes perforate, and diverticula of course do.

The cervical lymph node must have been pathologic. It was apparently a single mass, suggestive of involvement of one of the lymph nodes with carcinoma or some other malignant tumor, possibly lymphoma. Could it have been related to anything within the abdomen? The Virchow node, which we read about in textbooks but rarely see, does occur in carcinoma of the stomach and esophagus, sometimes occasionally from other abdominal carcinomas but not very frequently.

No peristalsis was heard except during paroxysms of pain, when a few, scattered, high-pitched sounds were audible. That is an important observation. After twenty-four hours of peritonitis it is a little bit unusual for a patient still to have peristalsis detected by auscultatory methods. One occasionally hears it, but it is distinctly unusual.

The tender mass in the pelvis is of interest. The average malignant tumor in the pelvis arising from the genital tract is not particularly tender. On the other hand, if one has a carcinoma arising in the bowel, it may well be tender because of secondary inflammation from infection. This could have been, I presume, a purely inflammatory mass.

This patient died, obviously of peritonitis, sixty-four hours after the sudden episode of pain and distention. Can we connect this whole history and try to make one diagnosis, or do we have to make several diagnoses? I am inclined to make more than one, but I must confess I do not know what exactly was wrong with her. I think it is fair to say, on the basis of the history, that she must have had gallstones and difficulty with the gall bladder because of certain aspects of the history, such as intermittent colicky pain in the upper abdomen. The fact that this followed a period of jaundice and that when it occurred the jaundice disappeared lends a certain amount of weight to the possibility of gallstone ileus. She may have had a large stone, which had entered the intestinal tract and passed down slowly, causing intermittent attacks of pain, and had ultimately lodged. I cannot remember a case of gallstone ileus in which a stone of sufficient size to obstruct the small bowel had passed through the common duct. Those that I am familiar with had ulcerated through into the abdominal cavity from the common duct across an abscess or an area of necrosis into the duodenum or from the gall bladder directly into the duodenum. Dr. Mallory perhaps would like to comment on that as a generality. But it seems to me that if we are dealing with gallstone ileus, which should be thought of, a more definite, acute, inflammatory process in the right upper quadrant should have been observed at some time or other in the past. We have no such observation. The only symptoms and signs that point toward the gall bladder are those of obstruction and not inflammation. So, although it possibly should be mentioned, on the basis of the history it seems to me that that diagnosis does not have sufficient weight.

Another important question to decide is whether the peritonitis that the patient died of arose as a result of the enema. One would think so from the way the history reads. She was all right except that the bowels did not move for twenty-four hours, which does not seem unusual, but she was given an enema and then the abdomen immediately became distended and she developed pain, which suggests perforation. Let us assume that the peritonitis did arise from perforation of the colon. I do not believe it came from perforation of the small bowel by the way of an enema. If the perforation and the peritonitis were the result of an enema, it must have been from the colon. Therefore, one would have to assume that there was some intrinsic lesion in the colon. The gall-bladder disease with jaundice, with some of the other things the patient had, and the type of pain, which was entirely in the upper abdomen, suggest either small-bowel obstruction or pancreatitis or perhaps gall-bladder colic. She probably had a mass in the pelvis. This mass was tender and irregular. It could have been malignant in the sense that it was a malignant neoplasm and it could of course have arisen in the bowel, in the sigmoid or in some other loop that lay within the pelvis. There is nothing to suggest that it arose from the retained cervix, which felt normal, though on motion of the cervix the patient experienced pain.

That is as far as I can go with a situation such as this. If we assume that the peritonitis, which she died of, arose as a result of the giving of an enema, I think we must also assume that she had some lesion of the colon, possibly the sigmoid, and that it probably was inflammatory, either primarily inflammatory or a growth of some kind that was secondarily inflamed. If we assume that that was the case, we have to neglect some of the important aspects of the history that have to do with the gall bladder.

Dr. Daniel S. Ellis: I should like to ask Dr. Sweet if he would consider the possibility of a malignant lesion perhaps involving the pancreas or the

ampulla of Vater as a cause of the pain rather than stone.

Dr. Sweet: I neglected to mention it, though it ran through my mind as I read the history over. I tried to explain the pain in the back and also the change in the picture that was characteristic of the appearance of that pain and prolonged nausea, which often occurs in pancreatic disease. Carcinoma of the pancreas may cause intermittent jaundice, so we need not exclude the diagnosis of carcinoma of the pancreas because of the fact that the jaundice cleared. Of course the lymph node in the neck, if it was malignant, could have been secondary to carcinoma of the pancreas as well as to other things — the lymphatic channels intercommunicate.

Dr. Ellis: One might also explain the hyperglycemia on that basis.

Dr. Sweet: That was a rather sudden development, was it not?

Dr. Ellis: I thought it was carcinoma of the pancreas or even of the ampulla of Vater, causing the onset of diabetes along with the onset of the original symptoms. In 2 cases that I know of, disappearance of symptoms, including the diabetes, was noted when the major lesion was detected.

Dr. W. Philip Giddings: We had this patient as a private case for a short period. She was brought here from another hospital, where the enema had been given. She had a normal gastrointestinal series and a negative barium enema, both within a few weeks. According to the patient, the interval between the enema and the distention and discomfort was very brief. But according to those who gave the enema and the doctor in the other hospital, there had been a distinct interval, and the onset of the change was by no means sudden or agonizing. On that basis I was inclined to believe that it was not perforation of the colon. We all thought that she had a perfectly good history of gall-bladder disease, and we thought that stones were present. The lymph node in the neck, which was a little above the supraclavicular area, actually was very hard, and there was no question in our minds that it represented a metastatic cancer. We questioned gallstone ileus as Dr. Sweet did, but it did not seem to fit. She had been under continuous medical observation for eight months, and we were informed that the diabetes had developed suddenly; on that basis and because of the node in the neck, we thought that we were dealing with carcinoma of the pancreas. The presence of peristalsis when she first came in did not seem compatible with peritonitis of twenty-four hours' duration, as it did not to Dr. Sweet. Our original impression was that she had abdominal carcinomatosis from carcinoma of the pancreas. The terminal event that started four hours after admission was rather dramatic. The passage into shock was very rapid. The increase in abdominal tenderness was very marked, and the rebound tenderness and so forth described did not appear until the final severe episode, but at that time it became apparent to us that she obviously had peritonitis as well and we were unable to state its source.

Clinical Diagnoses

Rupture of abdominal viscus.
General peritonitis.
Carcinoma of stomach?
Carcinoma of pancreas?

Dr. Sweet's Diagnosis

Generalized peritonitis from perforation of colon at site of inflammatory, malignant lesion.

Anatomical Diagnoses

Adenocarcinoma of pancreas, with metastases.
Perforation of metastatic carcinoma of ileum forming pelvic abscess.
Peritonitis, acute generalized.

Pathological Discussion

Dr. Tracy B. Mallory: When the peritoneal cavity was opened there was obvious diffuse peritonitis, which, because of the slight turbidity of the fluid, appeared quite fresh. In the pelvis there was a partially localized collection of pus that seemed to have been present for a rather longer time, perhaps for weeks even. On examining the bowel we found multiple tumor nodules, all of which, however, seemed to be involving the bowel from the serosa inward. The distribution was rather peculiar. One of these nodules had almost completely encircled the pylorus, producing quite marked pyloric stenosis. A second was in the ileocecal valve and likewise was quite stenotic. She had a Meckel diverticulum, but it was not perforated. About halfway between the Meckel diverticulum and the ileocecal valve was a perforation about 0.5 cm. in diameter in one of these multiple neoplastic areas. Further search showed that the primary carcinoma was in the pancreas. Approximately three quarters of the organ was destroyed by tumor. The gall bladder was dilated and thin-walled, and we found no stones in the gall bladder or bile duct. So we believe everything is explained by carcinoma of the pancreas and the metastases. I cannot say whether or not the enema had anything to do with the perforation in the small bowel, which was a considerable distance above the ileocecal valve — probably not.

Dr. Giddings: I believe, Dr. Mallory, that there was one more interesting feature about the autopsy — the site of the perforation in the ileum was in a loop that was fairly adherent in the right pelvis as the result of an old, fibrous band, which was pretty obviously a result of the hysterectomy.

Dr. Mallory: Yes. The bowel was sharply angulated, and the tumor nodule was in the site of the angulation, with the perforation in that knuckle. Whether that mechanical fixation had anything to do with the metastasis at that point is questionable.

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FAMILY REUNION

Massachusetts, the Mother of many outstanding figures and accomplishments in public health, will be able to view her children and see how they have developed when the American Public Health Association celebrates its seventy-sixth birthday with a meeting in Mechanics Hall, Boston, from November 8 to 12.

Just a hundred years ago the Massachusetts Medical Society was joining the American Statistical Association in petitioning the Legislature to establish a commission to survey sanitary conditions within the Commonwealth. The immediate result was the masterly report of Lemuel Shattuck and his associates, submitted April 25, 1850, and ultimately the first state board of health, with which Massachusetts set the pattern for the whole country nineteen years later.

The continued Massachusetts contribution is highlighted in the current presiding officers of the American Public Health Association. The president and first woman to hold this office, Dr. Martha Eliot, associate chief of the Children's Bureau, comes of a distinguished Boston family to which she adds lustre. The president-elect is Dr. Charles F. Wilinsky, an authority who has made himself indispensable locally and nationally in both public-health and hospital fields. His official positions as director of the Beth Israel Hospital and deputy commissioner of the Boston Health Department give only an indication of his broad community service.

The American Public Health Association has become a very influential and representative organization of twelve thousand members including professional workers in all branches of public health. Twelve sections will be holding scientific sessions, and a great many discussions will vitally interest practicing physicians. A special session honoring Lemuel Shattuck will be held on November 10.

During the twenty-five years since the American Public Health Association last met in Boston public health has developed enormously. As the mother of so much of the best in public health, Massachusetts has a tremendous interest in seeing what manner of men her children have become. Her cordial greeting will be heightened by a maternal interest in how the offspring have fared in other environments and, as children returning from far places, in the new ideas they will doubtless introduce into the "home."

DIAMOND ANNIVERSARY OF NURSING

Nursing Progress Week, beginning on November 14, has long been in preparation. In planning for it the American Nurses' Association has done a truly admirable piece of work, organizing a nation-wide demonstration that will reach its peak on Linda Richards Day, November 16. It deserves the nation's attention.

Nursing, in one form or another, is an ancient calling, devoted to the care of those who cannot

care for themselves. It was a group activity, semi-organized, and largely on a religious basis before the Middle Ages. It was not until the early nineteenth century that the roots of modern training struck into fertile soil at Kaiserswerth, under the guidance of Pastor Fliedner, and it was here that Florence Nightingale found the inspiration that was to be her own lifelong guiding influence. Nursing became a profession when she later organized the school at St. Thomas' Hospital in London.

In America the first professional school for nursing was established in 1872 in Boston, at the New England Hospital for Women and Children. Linda Richards was its first matriculant and in the following year became America's first graduate nurse. In 1873 schools for nurses were established at Bellevue Hospital in New York, where Linda Richards, after her graduation, became night superintendent; at the Massachusetts General Hospital; and at New Haven, Connecticut, where the Connecticut Training School for Nurses came into existence.

The "Boston Training School" as it was first called, which had been established at the Massachusetts General Hospital, welcomed Linda Richards as its own superintendent in 1874. In 1877 she went to England to study nursing methods in the school at St. Thomas', returning in the same year to organize the training school at the Boston City Hospital.

So it is that in 1948, seventy-five years after the first trained nurse was graduated and these three eminent schools of nursing were founded, the Diamond Jubilee of Nursing in America is appropriately celebrated.

There must be other purposes for a jubilee than the recapitulation, however proudly, of seventy-five years of progress by a profession. The American Nurses' Association, with 162,000 of the 320,000 registered nurses in America in its membership, has set itself to the recruitment of the 40,000 additional students needed for approved schools. It is directing attention to the necessity for the extension and improvement of nursing service to all through the improvement of schools of nursing. It is promoting "economic security for all nurses, adequate licensure laws and more effective counseling and placement of both prospective students and graduate nurses."

Thus the struggle goes on for all groups, seeking higher standards of achievement and better standards of working and living. The problem that still defies solution is the basic economic one of payment and where it is to come from.

MANUSCRIPTS AND MEDICAL HISTORY

Manuscripts are the source material of medical history. Occurring in the form of diaries, account books, case records, biographical collections and single items, letters, bills, recipes, treatises and miscellaneous documents of all periods, including the present, they should be preserved and deposited in permanent sanctuaries for the benefit of scholars and other interested persons.

The correspondence and other documents of eminent physicians of the twentieth century will be valuable to the people of the succeeding centuries, throwing light upon medicine of today in its economic, social and clinical aspects.

Single letters may be of the greatest importance, such as the letter of Dr. Zadok Howe, written in 1814 to Dr. Nathaniel Miller on the prospectus of the cancer hospital at Franklin, Massachusetts; and the three letters of Dr. Oliver Wendell Holmes written in 1861 and 1863, relating to the injury received by his son, later Justice Holmes, at Keedysville during the Civil War. Recently the Boston Medical Library has acquired a collection of twenty-two letters of Dr. Howe that throw considerable light upon his personality and character.

Physicians from time to time have collected letters of eminent medical men and have eventually deposited their collections in medical and historical libraries. Dr. Ernest B. Young, of Boston, made such a collection and gave it to the Boston Medical Library before his death in 1923. Dr. Lyman Spalding, of Maine, who lived from 1775 to 1821, was an eminent physician of his time and corresponded with the outstanding physicians of the country. He wrote the first edition of the *Pharmacopoeia of the United States of America*, published in Boston in 1820. His letters and scrapbook and the manuscript of the *Pharmacopoeia* descended to his grand-

son, Dr. James A. Spalding, who presented the collection to the Boston Medical Library.

The Library has also been the recipient of many outstanding gifts from public-spirited citizens who believed in placing valuable documents in local institutions where they could be properly safeguarded and preserved for posterity.

In this connection there may be noted the receipt book, dated 1643, of Governor John Winthrop of Massachusetts; a collection of medical letters, written between 1652 and 1663, of his son, John Winthrop, governor of Connecticut; the documents of Dr. James Thacher, of Plymouth, covering the years from 1754 to 1844, and recently supplemented by a collection of twenty-three letters; the original records of the secretary of the Milton Vaccination Committee, dated 1809, giving in detail the story of the famous experiment of inoculation and vaccination of the children of the town; the records of inoculations and vaccinations from 1775 to 1800, at Rainsford Island, in Boston Harbor; and the original depositions of various prominent physicians and other persons given in Suffolk Superior Court in 1853 on the petition of William T. G. Morton, regarding his right to use ether as a surgical anesthetic, and other valuable documents that have found a permanent abode in the Library.

Where material of local value cannot be obtained by gift, every effort should be made to acquire it by purchase. Booksellers and book scouts occasionally come into possession of such material and usually offer it to local libraries or societies. It is regretted that some institutions do not recognize the necessity of owning all documents of local interest and, rather than spend a few dollars, permit the material to go elsewhere.

Dr. Spalding was a good friend of the Boston Medical Library, and it was through his efforts that the collection of original sketches and drawings of the anatomist, Alexander Ramsey, made between 1721 and 1824, were rescued from a closet in a New Hampshire farmhouse. The director of the Library recalls driving one brisk October morning to Portland, Maine, to see Dr. Spalding, and then driving another hundred miles into the mountains and having to listen to a broadcast of a world-series game before any business could be transacted, reminding one of tea-time and the Saturday holiday in London, where likewise business cannot be considered during these sacred hours. However, negotiations were conducted satisfactorily, and the drawings are now in Boston.

Dr. Frederick C. Shattuck, 1847-1929, a prominent physician of Boston, with a national reputation, saved all the letters received by him from other physicians throughout the country and from time to time turned them over to the Library. Such letters are valuable for their contents or their signatures, and all such current correspondence unless privileged should be preserved and presented to local institutions.

Dr. H. Winnett Orr, the eminent orthopedic surgeon of Lincoln, Nebraska, who invented the Orr method of treating osteomyelitis, is also historically minded. He systematically assembled in fifteen folio scrapbooks a mass of material on his personal and family affairs, on the history of orthopedics and on osteomyelitis, wound treatment and fractures. Volume Six constitutes a history of the first American orthopedic unit to England and France from 1917 to 1919. In 1921 Dr. Orr wrote an interesting pamphlet entitled *An Orthopedic Surgeon's Story of the Great War*. The scrapbook of 365 pages contains a mass of documentary and photographic material relating to the unit. In the back there is a long manuscript by Dr. Orr on the history of the orthopedic service of Base Hospital No. 8, American Expeditionary Forces. Dr. Orr, recognizing the outstanding local importance of his scrapbook, very generously presented it to the Boston Medical Library. It is hoped that in the future all documentary material relating to the medical profession in any way will be preserved and deposited with appropriate libraries or institutions.

LO, THE POOR ESKIMO

A BCG-vaccination program among the Eskimos at Point Barrow, Alaska, has been completed, according to the Bureau of Indian Affairs. The initiation of a medical survey on Navajo-Hopi reservations in Arizona and New Mexico, conducted by a team selected by the American Medical Association, under the leadership of Dr. Louis J. Moorman, of

Oklahoma City, is also reported from the same source.

Other medical surveys under similar federal and American Medical Association auspices have been completed in Alaska and on Indian reservations of the Northwest, the *Washington Report on the Medical Sciences* announces. Another is planned for Puerto Rico. Since the incidence of tuberculosis among Alaskan natives is recorded as sixteen times as high as the rate for the continental United States, it is comforting to know that the continent's oldest inhabitants currently receive more tangible evidence of their adopted country's esteem than souvenir canes.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR SEPTEMBER, 1948

RÉSUMÉ

DISEASE	SEPTEMBER 1948	SEPTEMBER 1947	SEVEN-YEAR MEDIAN
Chancroid	2	2	1*
Chicken pox	135	123	110
Diphtheria	28	10	10
Dog bite	1005	942	924
Dysentery, bacillary	9	13	13
German measles	58	43	49
Gonorrhea	303	393	410
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	0	0*
Malaria	1	7	13
Measles	203	69	150
Meningitis, meningococcal	5	3	8
Meningitis, Pfeiffer bacillus	2	0	0
Meningitis, pneumococcal	1	1	1†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	1	1	0†
Meningitis, other forms	0	0	0†
Meningitis, undetermined	6	12	3†
Mumps	351	148	194
Pneumonia, lobar	276	31	66
Poliomyelitis	55	147	121
Salmonellosis	2	26	20
Scarlet fever	107	130	241
Syphilis	141	206	361
Tuberculosis, pulmonary	203	217	217
Tuberculosis, other forms	15	16	16
Typhoid fever	1	1	3
Undulant fever	4	10	2
Whooping cough	268	644	546

*Four-year median.

†Six-year median.

COMMENT

Diseases with an incidence above the seven-year median were chicken pox, diphtheria, German measles, measles, mumps, lobar pneumonia and undulant fever.

Diseases with an incidence below the seven-year median were bacillary dysentery, meningitis, poliomyelitis, scarlet fever and whooping cough.

Mumps was again at the highest level since it was made reportable in 1916. Poliomyelitis was at the lowest since 1942.

There is still too much diphtheria. The majority of the cases were in unimmunized persons. Some were in persons who had failed to have booster doses.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Actinomycosis was reported from: Everett, 1; total, 1.

Diphtheria was reported from: Arlington, 4; Athol, 1; Boston, 19; Brookline, 1; Cambridge, 1; Lawrence, 1; Montague, 1; total, 28.

Dysentery, bacillary, was reported from: Boston, 1; Fitchburg, 1; Holyoke, 1; Lowell, 3; Worcester, 2; Wrentham, 1; total, 9.

Encephalitis, infectious, was reported from: Worcester, 2; total, 2.

Lymphocytic choriomeningitis was reported from: Cambridge, 1; Danvers, 1; Fitchburg, 7; total, 9.

Malaria was reported from: Swansea, 1; total, 1.

Meningitis meningococcal, was reported from: Boston, 1; Brookline, 1; Cambridge, 1; Lynn, 1; Quincy, 1; total, 5.

Meningitis, Pfeiffer bacillus, was reported from: Holyoke, 1; South Hadley, 1; total, 2.

Meningitis, pneumococcal, was reported from: Boston, 1; total, 1.

Meningitis, streptococcal, was reported from: Groton, 1; total, 1.

Meningitis, undetermined, was reported from: Ashburnham, 1; Brockton, 1; Cambridge, 1; Chicopee, 1; Plainville, 1; Stoughton, 1; total, 6.

Poliomyelitis was reported from: Agawam, 1; Arlington, 1; Barnstable, 1; Belmont, 1; Boston, 6; Cambridge, 2; Carver, 1; Chicopee, 1; Dartmouth, 1; Everett, 2; Framingham, 1; Hinsdale, 1; Leominster, 1; Lexington, 1; Mansfield, 1; Marblehead, 1; Marlboro, 1; Millbury, 1; New Bedford, 1; Newton, 2; Northampton, 1; Pittsfield, 1; Princeton, 1; Rockport, 1; Salem, 1; Salisbury, 1; Springfield, 9; Walpole, 1; Watertown, 2; West Boylston, 2; West Springfield, 2; Woburn, 1; Worcester, 4; total, 55.

Salmonellosis was reported from: Beverly, 1; Worcester, 1; total, 2.

Septic sore throat was reported from: Boston, 2; Chelsea, 1; Newton, 1; total, 4.

Trichinosis was reported from: Methuen, 1; Swansea, 1; Watertown, 1; total, 3.

Typhoid fever was reported from: Fall River, 1; total, 1.

Undulant fever was reported from: Bridgewater, 1; Marblehead, 1; Rehoboth, 1; Templeton, 1; total, 4.

MISCELLANY

TRAINED FISH

Scientists at the University of Wisconsin, according to a recent news release, are training fish to smell. Such a course would be considered unnecessary on the Atlantic seaboard – classed with carrying coals to Newcastle.

Actually, the bluntnose minnow, in contradiction to its descriptive name, has been found to have an unusually keen sense of smell. It can detect phenols in water in low concentrations and, with the use of electric shocks to condition its reflex, has been taught to react in an agitated manner when the offending substance is encountered.

MEDICAL DIRECTOR OF NEW ENGLAND TELEPHONE AND TELEGRAPH COMPANY

Dr. George F. Wilkins, of Brookline, a native of Kinderhook, New York, and a graduate of Holy Cross College and Harvard Medical School, has been appointed medical director of the New England Telephone and Telegraph Company.

OLD MAN OF THE SEA

If the Federal Security Administration figures on births and longevity are reasonably reliable, 21,500,000 of the nation's population will be sixty-five years of age or over by century's end, *Insurance Economics Surveys* reports. With a steadily decreasing number of employable citizens the social-security burden of the future can be left to the imagination.

NATIONAL MENTAL HEALTH ACT

In the year since funds were made available under the National Mental Health Act of 1946, Government-supported programs have been activated in forty-two states and the four territories, according to a report from *Scientific American*. The six remaining states are in process of setting up their programs.

BOOK REVIEWS

The Treatment of Rheumatism in General Practice. By W. S. C. Copeman, O.B.E., M.A., M.D. (Cantab.), F.R.C.P. (London). Fourth edition. 8°, cloth, 258 pp. Baltimore: Williams and Wilkins Company, 1946. $4.00.

This small volume, written for the general practitioner, has the virtue of brevity and clarity. It presents the accepted British teaching on rheumatism, which differs somewhat from the American point of view. Although treatment is discussed fully there is too much of a recital of remedies without any critical evaluation of these remedies. The book would have been greatly improved by tables or outlines of treatment that the author advocates. Illustrations would also have added to the teaching value of the work.

Case Histories in Clinical and Abnormal Psychology. Edited by Arthur Burton. 8°, cloth, 680 pp. New York and London: Harper and Brothers, 1947. $4.00.

This book, although primarily intended as a case book to accompany courses in abnormal psychology, might be of interest to others, such as psychiatrists, general practitioners and certain laymen. The work consists of case histories of varying importance indicative of prevailing psychologic methods in the United States.

Besides the value of the case histories themselves, one gets a vivid example of the usefulness of psychologic testing so far as diagnosis, prognosis and treatment are concerned.

The various papers are an excellent example of scientific reporting, and although each has some special merits, the usefulness of the Rorschach test in depicting various tendencies even when overt signs are absent was of particular interest to the reviewer.

To the general reader this book will undoubtedly demonstrate the importance of the clinical psychologist in evaluating emotional problems — a fact long recognized by psychiatrists.

Hormones and Behavior: A survey of interrelationships between endocrine secretions and patterns of overt response. By Frank A. Beach. With a foreword by Earl T. Engle. 8°, cloth, 368 pp. New York: Paul B. Hoeber, Incorporated, 1948. $6.50.

This work is a detailed, encyclopedic account of the problems concerning the interrelation of hormones and overt behavior. The author has gone to considerable lengths to include a great number of experimental data and has compiled a volume that may be considered unique of its kind. He has included most of the important work done on this subject and has presented it in a well systematized manner. Because of the peculiar nature of the studies, the author has limited himself in great part to a recitation of the known facts and has only attempted to draw general conclusions therefrom.

The major interest of this work is for those who are especially concerned with experimental approach to the problem of hormonal influence on behavior; however, it can be classed among books that will always be of value in any library as a reference work for anyone concerned with behavior in general.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Interesting and Useful Medical Statistics. Edited by William H. Kupper, M.D. 8°, cloth, 528 pp. Dubuque, Iowa: William C. Brown Company, 1948. $6.50.

In this unusual book the compiler has presented numerous statistical tables on morbidity and mortality, on the incidence of symptoms, signs, results of treatment of disease and on miscellaneous subjects of medical interest, such as absenteeism, atomic bomb victims, contraception, dicumarol, drivers, farm and Fourth of July accidents, life expectation, male climacteric, medical education, Negro physicians, smoking, state boards, UNRRA personnel and weights of men. The tables have been selected from the literature of the past ten years and comprise two hundred and twenty-five topics arranged alphabetically. Full acknowledgment is given to the original publisher. The volume is recommended as an essential reference tool for all medical and general libraries.

Epilepsy. Proceedings of the Association held jointly with the International League against Epilepsy, December 13 and 14, 1946, New York. 8°, cloth, 654 pp., with 167 illustrations and 56 tables. Baltimore: Williams and Wilkins Company, 1947. $12.00.

This volume comprises the twenty-sixth of the *Research Publications of the Association for Research in Nervous and Mental Disease.* Eighty-two persons have contributed to the volume, comprising forty-five papers. The text is divided into seven parts: historical; heredity and pathology; experimental studies; electroencephalography; medical treatment; war and epilepsy; and psychological-social. A good index concludes the text. The publishing is excellent. The book should be in all medical libraries and in the collections of all physicians interested in the subject.

Physical Treatment of Injuries of the Brain and Allied Nervous Disorders. By K. M. Hern, M.C.S.P., diplomate of Liverpool Physical Training College, in charge of physiotherapy, Department of Military Hospital for Head Injuries, Oxford. With a foreword by Air Vice-Marshal Sir Charles P. Symonds, K.B.E., C.B., D.M., F.R.C.P. 8°, cloth, 96 pp., with 83 illustrations. Baltimore: Williams and Wilkins Company, 1947. $4.00.

This monograph describes the method of treatment employed in the Military Hospital for Head Injuries, Oxford, England. In this method the patient and physiotherapist co-operate. The monograph is well printed and should prove useful to all persons interested in the subject.

Noah Webster: Letters on yellow fever addressed to Dr. William Currie. With an introductory essay by Benjamin Spector, M.D. 8°, paper, 110 pp., with one portrait. Baltimore: Johns Hopkins Press, 1947. $2.00. Supplements to the *Bulletin of the History of Medicine.*

Dr. Spector in this monograph has made a noteworthy contribution to American medical history. Noah Webster, generally thought of as a lexicographer, was an epidemiologist of no mean stature and the author of a two-volume treatise on epidemic and pestilential diseases published at Hartford in 1799. Dr. William Currie was a highly respected physician of Philadelphia. He became interested in yellow fever prevalent in his city in 1797 and wrote a series of letters to Benjamin Wyncoop that were published in a local newspaper. The series of twenty-five letters by Webster were addressed to Dr. Currie and likewise published in a newspaper the *Commercial Advertiser*, New York, during the months of October to December, 1797. In his introductory essay Dr. Spector discusses Webster's contribution to American medical thought and progress and analyzes his work on infectious diseases. A table of contents summarizes the various letters. The monograph is well published in every way. An index, although difficult to compile, would have been a valuable addition to the text. The volume is recommended for all medical and general history collections.

Identification of Tumors: Essential gross and microscopic pathologic features systematically arranged for easier identification. By N. Chandler Foot, M.D., professor of surgical pathology, Cornell University Medical College, and surgical pathologist to New York Hospital. 8°, cloth, 397 pp., with 241 illustrations and 26 tables. Philadelphia: J. B. Lippincott Company, 1948. $6.00.

In this volume Dr. Foot has presented a guide to the identification of tumors, malignant and benign, illustrated with photomicrographs. The text is divided into two parts: neo-

plasms of general distribution, and neoplasms of special systems and organs, including a chapter on the ear and eye. The text is concluded with two special chapters on the technical methods of value in the diagnosis of tumors and a tabular locator for tentative identification of neoplasms. A good index concludes the volume. The illustrations are excellent, clear and well defined. The type is large and clear, and the printing well done. The book should prove valuable to students, surgeons and physicians.

Handbook of Treatment and Medical Formulary. By Charles M. Gruber, M.D., professor of pharmacology, Jefferson Medical College, Philadelphia. 8°, cloth, 585 pp. Philadelphia: F. A. Davis Company, 1948. $7.00.

Dr. Gruber has written this manual for the general practitioner and under each disease gives condensed methods of treatment and dosages in metric and apothecaries' measures, of the recommended remedies. The material is arranged alphabetically. A valuable appendix of sixty pages lists important drugs, galenical preparations and chemicals with average doses. There is a good index. The manual should prove valuable to the practicing physician as a quick reference source.

Synopsis of Pediatrics. By John Zahorsky, M.D., professor of pediatrics and director, Department of Pediatrics, St. Louis University of Medicine, and pediatrician-in-chief to the St. Mary's Group Hospitals. Assisted by T. S. Zahorsky, M.D., senior instructor in pediatrics, St. Louis University School of Medicine, and assistant pediatrician to the St. Mary's Group of Hospitals. Fifth edition. 12°, cloth, 449 pp., with 158 text illustrations and 9 color plates. St. Louis: C. V. Mosby Company, 1948. $5.50.

This edition of a standard manual, intended primarily for students, first published in 1934, has been thoroughly revised and enlarged to some extent. Material on the newer drugs has been incorporated in the text. A good index concludes the volume. The manual should prove useful to students and general practitioners. The publishing is excellent, although the type is of a small size necessitated by the size of the volume and the amount of text.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, November 9, at 8 p.m. The Department of Biological Chemistry, Harvard Medical School, will present the following program:

The Production of Radioactive Cystine by Direct Bombardment in the Pile. Eric G. Ball, Arthur K. Solomon and Octavia Cooper.

Ascorbic Acid and the Biologic Action of Adrenal Cortical Hormones. Ralph W. McKee, Theodore S. Cobbey, Jr., and Quentin M. Geiman.

Metabolism of C^{14}-Labeled Glucose by the Rat Diaphragm in Vitro. Claude A. Villee.

Isotopic Studies of the Origins of Glycogen Carbons. A. Baird Hastings and Yale J. Topper.

Localization of Cerebral Tumors Employing P^{32}. Bertram Selverstone, Arthur K. Solomon and William H. Sweet.

Subsequent meetings will be held on December 14, January 11, February 8, March 8, April 12 and May 10.

NEW ENGLAND CONFERENCE OF INDUSTRIAL PHYSICIANS AND SURGEONS

The yearly dinner meeting, with election of officers, of the New England Conference of Industrial Physicians and Surgeons will be held at the University Club, Boston, on November 10, at 6:00 p.m. Colonel W. C. Knott, M.C., U.S.A., will speak after the dinner on the subject "What the United States Army is doing in Industrial Medical Work."

AMERICAN ACADEMY OF GENERAL PRACTICE

The first annual scientific assembly of the American Academy of General Practice will be held at the Netherlands Plaza Hotel, Cincinnati, Ohio, March 7 to 9. The program will include essays by eighteen outstanding medical teachers, a dinner for secretaries and presidents of constituent state chapters and a banquet for members and their wives and guests.

Nonmembers of the Academy may attend the assembly as guests on payment of a registration fee of $5.00 (only doctors of medicine may register). There is no registration fee for members. Banquet tickets will be sold at $5.00 a plate.

Members wishing to make hotel reservations may apply to the chairman, Sub-Committee on Hotels, American Academy of General Practice, Dixie Terminal Building, Cincinnati 2, Ohio.

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The seventh annual meeting of the American Academy of Dermatology and Syphilology will be held in Chicago December 4 through 9.

The principal sessions will be held at the Palmer House, with special courses in histopathology and mycology scheduled for Saturday and Sunday, December 4 and 5, at the Medical Schools of the University of Illinois and Northwestern University. As in the past two years, teaching clinics will be held on the afternoons of Monday, Tuesday and Wednesday, December 6, 7 and 8. A new feature this year consists of informal discussion groups, which will be held at noon and 5:00 p.m.

Extensive scientific and technical exhibits will be set up. Dr. Samuel M. Bluefarb is chairman of the committee on scientific exhibits, and Dr. Clyde L. Cummer is in charge of the technical exhibits.

Special courses in histopathology, mycology, x-ray and radium therapy, mucous-membrane lesions, bacteriology of the skin, industrial dermatoses, specific granulomas and dermatoscleroses will be held under leaders in these various fields.

Special lectures will be given on: "Certain Aspects of Blood Dyscrasias of Special Interest to Dermatologists," by Dr. Cyrus C. Sturgis, chairman, Department of Internal Medicine, Medical School, University of Michigan; "The Relation of Endocrines to Cutaneous Diseases," by Dr. Arthur A. Hellbaum, professor of pharmacology, School of Medicine, University of Oklahoma, and Dr. E. C. Keaty, research associate of pharmacology and dermatology, School of Medicine, University of Oklahoma.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 11

FRIDAY, NOVEMBER 12

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*12:00 m. Clinicopathological Conference. Margaret Jewett Hall. Mt. Auburn Hospital, Cambridge.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

MONDAY, NOVEMBER 15

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, NOVEMBER 16

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.

WEDNESDAY, NOVEMBER 17

*11:00 a.m.–12:00 m. Medical Rounds. Amphitheater, Children's Hospital.

*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

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*Open to the medical profession.

(*Notices concluded on page xv*)